World Health Organisation

Essential Medicines List for Children (EMLc); Palliative Care

CONSULTATION DOCUMENT

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ABSTRACT

Background

The World Health Organization (WHO) Essential Medicines List for Children (EMLc) aims to promote worldwide equity of access to essential medicines for children and is based on the criteria of safety, efficacy and cost effectiveness. The current EMLc does not include specific recommendations for paediatric palliative care. A review of the EMLc was proposed to ensure access to appropriate medicines for pharmacological management of the most prevalent and distressing symptoms in children with life threatening and life limiting (Life shortening) conditions worldwide.

Objectives

- To identify the most important symptoms for paediatric palliative care taking into account prevalence and associated distress
- To identify appropriate pharmacological approaches for management of individual symptoms
- To determine effectiveness and safety of identified pharmacological approaches

Methods

Worldwide childhood mortality national data was identified through internet searching of relevant websites and databases: World Health Organisation Mortality Database, Demographic and Health Surveys and UNICEF. Representative data was then extracted to identify the most common causes of death from life threatening and life limiting conditions in infancy, childhood and adolescence.

An electronic search of MEDLINE (1966 – May 2008) and EMBASE (1980 – May 2008) together with hand searching identified articles and target journals was used to identify incidence, prevalence and suffering from specific symptoms in children and young adults aged 0 – 24 years, with life threatening and life limiting conditions.

A further literature search, using the same strategy supplemented by searching databases of evidence based review and evidence based guidelines was undertaken to identify evidence to support the pharmacological management of these symptoms. Meta-analyses, systematic reviews or good quality randomised controlled trials specific to the pharmacological management of the identified symptom in paediatric palliative care were sought

Each symptom was presented in a monograph with supporting references and SIGN level of evidence

Main results

There was a lack of accurate data on childhood mortality from life threatening and life limiting conditions particularly in resource poor settings. However malignancy and HIV/AIDS were clearly identified as the most common worldwide causes of childhood mortality appropriate to palliative care.

No high quality prospective studies of symptoms and associated distress, using validated reporting tools, in children receiving palliative care were identified. Available evidence comprised almost exclusively retrospective case-note reviews, retrospective interviews from staff and studies of bereaved parents. One prospective study using reports from professionals was identified. Analysis of available evidence suggested 10 key symptoms and symptom clusters that should be considered a priority for EMLc palliative care.

No high quality randomized controlled trials of symptom management in children receiving palliative care were identified. A number of systematic reviews of symptom management adult patients with malignancy receiving palliative care were identified. However, many of these reviews concluded that there was insufficient evidence to draw any firm conclusions. Several important medicines were identified that should be added to the EMLc in order to ensure access to appropriate pharmacological symptom control for children receiving palliative care. However research evidence to directly support these recommendations was generally weak.

Conclusions

Worldwide, malignancy and HIV/AIDS appear to be the most important diagnoses of children who require palliative care. Within these diagnostic groups there appear to be ten symptoms which are most important in terms of prevalence and suffering. Several important medicines were identified that should be added to the EMLc in order to ensure access to appropriate pharmacological symptom control for children receiving palliative care worldwide. However research evidence to directly support these recommendations was generally weak.

SUMMARY OF RECOMMENDATIONS

Proposed priority symptom list for WHO EMLc Palliative Care

- Fatigue and weakness
- Pain
- Anorexia and weight loss
- Delirium and agitation
- Breathlessness
- Nausea and vomiting
- Constipation
- Depression
- Excess respiratory tract secretions
- Anxiety

Fatigue and weakness

NO PHARMACOLOGICAL AGENT RECOMMENDED

- There are relatively few studies conducted to evaluate the use of psychostimulants in the management of fatigue in adult palliative care although there are some positive results. No evidence has been identified to support the use of psychostimulants for this indication in children and inclusion in the EMLc is not recommended.

- Very few studies have been conducted to evaluate the effectiveness of corticosteroids in the management of fatigue in adult palliative care and available evidence for use is weak. No evidence of use in children for this indication was identified.

Pain

Recommendations for Inclusion: PARACETAMOL, IBUPROFEN, CODEINE, MORPHINE, AMITRIPTYLINE, CARBAMAZEPINE, and DEXAMETHASONE

No new medicines for addition to EMLc as all of the above are currently included

New formulations for addition to EMLc:
Ibuprofen oral suspension 100mg/5ml
Codeine oral syrup 25mg/5ml
Morphine sulphate modified release granules 20mg, 30mg, 60mg, 100mg and 200mg
Amitriptyline oral tablets 10mg
Dexamethasone oral tablets 2mg

- There is good evidence and extensive experience of the use of paracetamol, ibuprofen, codeine and morphine in paediatric pain. These drugs are already included in the EMLc as analgesics.

- Morphine is the strong opioid of choice in moderate to severe pain and this is confirmed by a number of consensus guidelines. There is extensive clinical experience of its use in children and its use should be promoted to ensure adequate analgesia as necessary. The inclusion of both immediate release and sustained release oral

preparations is recommended to enable morphine to be successfully used in both acute and chronic pain.

- Although not specific to palliative care, good quality systematic reviews confirm the efficacy of adjunctive analgesic therapy with amitriptyline and carbamazepine in chronic neuropathic pain in adults. There is considerable experience of the use of these drugs in neuropathic pain and other indications in the paediatric population. Both these drugs are currently included in the EMLc for other indications and they are widely available worldwide with extensive safety data.

- Non-steroidal anti-inflammatory agents are considered the co-analgesic of choice for bony pain. There is insufficient evidence to support the use of one NSAID over another for this indication. Ibuprofen is already included in the EMLc and is an appropriate choice and there is evidence to support its safety and efficacy in children.

- Benzodiazepines are widely used as a co-analgesic to treat pain associated with skeletal muscle spasm. Diazepam has antispasticity action and is already included in EMLc for pre operative sedation and as an anticonvulsant for status epilepticus.

- Corticosteroids have demonstrable efficacy in the reduction of peritumour oedema. There is little good quality research evidence to support their use however consensus documents suggest they have a role in the reduction of pain due to raised intracranial pressure in central nervous system tumours and the treatment of neuropathic pain due to peripheral nerve compression. Dexamethasone is already included in EMLc for acute management of anaphylaxis and allergic reactions.

Anorexia and weight loss

NO PHARMACOLOGICAL AGENT RECOMMENDED

- A meta-analysis shows a benefit of megestrol acetate in adult patients with a clinical diagnosis of anorexia-cachexia related to cancer although there is insufficient evidence to define the optimal dose. However in children with cancer reports of profound adrenal suppression with megestrol acetate suggest that this drug needs to be used with caution. Inclusion of megestrol acetate in the EMLc is not recommended.

- A small number of adult studies suggest oral or parenteral corticosteroids may be of use in the short term management of anorexia in palliative care although the evidence base is weak. The optimal dose and duration is not known and no studies in children have been identified.

Delirium and terminal agitation

Recommendations for Inclusion: HALOPERIDOL AND MIDAZOLAM

New medicines for addition to EMLc: Midazolam

New formulations for addition to EMLc:
Midazolam injection 1mg/ml and 5mg/ml

- Effective management of delirium and agitation at end of life requires identification and treatment of the underlying cause(s)

- Haloperidol is widely used in the management of psychotic disorders in both the adult and child population. Haloperidol is considered the first choice therapy in the management of agitation associated with delirium in end of life care. There is randomised controlled trial evidence to support the use of haloperidol in management of delirium hospitalised adults with AIDs. Haloperidol is already included in the EMLc as an antipsychotic.

- Where agitation and terminal restlessness persists despite identification and treatment of possible underlying causes, expert opinion supports the use of benzodiazepines for their anxiolytic sedative properties. No evidence of improved efficacy or safety of one benzodiazepine over another was identified. The choice of benzodiazepine for inclusion in the EMLc for palliative care is therefore determined by the availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.

- Midazolam can be administered subcutaneously and as a continuous infusion with other medication for symptom management when the enteral route is no longer available. Midazolam can also be administered via the buccal route with rapid onset and ease of administration. There is evidence to support the safety of administration of midazolam via the buccal route in children.

Breathlessness (dyspnoea)

Recommendations for Inclusion: MORPHINE, DIAZEPAM AND MIDAZOLAM

New medicines for addition to EMLc: Midazolam

New formulations for addition to EMLc:
Morphine sulphate modified release granules 20mg, 30mg, 60mg, 100mg and 200mg
Midazolam injection 1mg/ml and 5mg/ml
Diazepam rectal tubes 2.5mg, 5mg and 10mg

- There is good quality evidence to show that morphine (oral and parenteral) is effective in the treatment of breathlessness in adult palliative care. These results can be appropriately extrapolated to children. Direct evidence of effectiveness in children is limited to case reports and expert opinion. Morphine is already included in the EMLc as an analgesic and use in breathlessness in palliative care is recommended.

- Anxiety is commonly associated with dyspnoea and benzodiazepines may be used as adjunctive therapy with morphine. No evidence of improved efficacy or safety of one benzodiazepine over another was identified. The choice of benzodiazepine for inclusion in the EMLc for palliative care is therefore determined by the availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.

- Diazepam is already included in EMLc for pre operative sedation and as an anticonvulsant for status epilepticus. Diazepam is appropriate for oral administration and has a relatively long half life appropriate for twice daily dosing.

- Midazolam can be administered subcutaneously and as a continuous infusion with other medication for symptom management when the enteral route is no longer available. Midazolam can also be administered via the buccal route with rapid onset and ease of administration. There is evidence to support the safety of administration of midazolam via the buccal route in children.

Nausea and vomiting

Recommendations for Inclusion: HALOPERIDOL, CYCLIZINE, METOCLOPRAMIDE, LEVOMEPROMAZINE,

New medicines for addition to EMLc: Cyclizine and Levomepromazine

New formulations for addition to EMLc:
Cyclizine oral tablets 50mg and injection 50mg/ml
Levomepromazine oral tablets 25mg and injection 25mg/ml

- The evidence base for the pharmacological treatment of nausea and vomiting in palliative care is weak and based largely on clinical experience and proven efficacy of these agents in other situations. It is suggested that if the cause of emesis is known or suspected, the choice of first line agent(s) should correlate with this cause. However, it is very likely that a combination of anti-emetics with complementary actions will be necessary.

- Haloperidol is a powerful D2 receptor antagonist and has antiemetic properties with actions on the area postrema. Haloperidol is recommended for the first line management of nausea and vomiting due to drug induced or metabolic causes. Haloperidol is already included in the EMLc as an antipsychotic. Haloperidol can be administered subcutaneously or intravenously as a continuous infusion with other medication for symptom management when the enteral route is no longer available.

- Cyclizine is an antihistaminic anti-muscarinic anti-emetic. It is considerably less sedating than diphenhydramine. It has a similar spectrum of action to promethazine but is considerably less sedating and can be used safely in combination with haloperidol. Cyclizine can be administered subcutaneously or intravenously as a continuous infusion with other medication for symptom management when the enteral route is no longer available. The inclusion of cyclizine is recommended for the first line management of nausea and vomiting due to stimulation of the vomiting centre due to raised intracranial pressure, efferent activity from stretch receptors in serosa of viscera or gastrointestinal mucosal irritation.

- Metoclopramide is a prokinetic antiemetic already included in EMLc. Metoclopramide is recommended for the first line management of nausea and vomiting associated with delayed gastric emptying.

- Levomepromazine has potent broad spectrum antiemetic properties and is less sedating than chlorpromazine at equivalent antiemetic doses. There is considerable experience of the use of levomepromazine in management of nausea and vomiting refractory to first line treatment in adult palliative care patients and to a lesser extent in paediatric palliative care. Levomepromazine can be administered subcutaneously and as a continuous infusion with other medication for symptom management when the enteral route is no longer available.

Constipation

Recommendations for Inclusion: SENNA, DOCUSATE SODIUM

New medicines for addition to EMLc: Docusate sodium

New formulations for addition to EMLc:
Docusate sodium oral capsules 100mg and oral solution 50mg/5ml
Senna oral syrup 7.5mg/5ml

- There is a lack of evidence to support the use of one laxative, or combination of laxatives over another. Expert opinion supports the use of a stimulant laxative as first line for the management of constipation in palliative care including opioid induced constipation. If a stimulant laxative alone is insufficient expert opinion supports the addition of a stool softener

- Senna is a stimulant laxative appropriate for use in children and is already included in the EMLc

- Docusate sodium is an appropriate faecal softening agent for use in children and is a recommended addition to the EMLc.

Depression

Recommendation for Inclusion: FLUOXETINE

No new medicines for addition to EMLc

No new formulations for addition to EMLc

- Fluoxetine is included in the EMLc as an antidepressant for children from 8 years of age. Systematic reviews have demonstrated that fluoxetine is effective in reducing depressive symptoms in both children and adolescents outside the palliative care setting. However the safety of the SSRIs in children and adolescents is not fully established. Fluoxetine has a prolonged time of onset before a therapeutic effect is established and this may limit its role in palliative care

- Although not specific to palliative care, data from a good quality systematic review suggests tricyclic antidepressant agents are not useful in treating depression in pre-pubertal children. There is marginal evidence to support the use of tricyclic antidepressants in the treatment of depression in adolescents although the magnitude of this effect is likely to be moderate at best.

- There is some evidence in adult palliative care that, in the short-term, psychostimulants can reduce the symptoms of depression in palliative care specifically when a rapid onset of action is required for short-term use. No studies were identified in children and no clinical experience of use of psychostimulants for this indication in children is reported.

Respiratory tract secretions

Recommendation for Inclusion: HYOSCINE HYDROBROMIDE

New medicines for addition to EMLc: Hyoscine hydrobromide

New formulations for addition to EMLc:
Hyoscine hydrobromide transdermal patch 1mg / 72 hours and injection
400 microgram/ml and 600 microgram/ml

- Expert opinion and case series support the use of antimuscuarinic agents in prevention of accumulation of respiratory tract secretions during the dying phase. There is no substantial evidence from systematic review that any intervention, be it pharmacological or non-pharmacological, is superior to placebo in the treatment of death rattle.

- Hyoscine hydrobromide is commonly used as an antimuscarinic agent to control excessive secretions in palliative care including in children and is widely available in the UK, USA and Australia. Hyoscine hydrobromide is available as transdermal patches and as a parenteral formulation for intravenous or subcutaneous administration.

- There is a lack of conclusive evidence to support the use of hyoscine butylbromide or glycopyrronium bromide in preference to hyoscine hydrobromide in the management of excess respiratory secretions at end of life.

Anxiety

Recommendations for Inclusion: DIAZEPAM AND MIDAZOLAM

New medicines for addition to EMLc: Midazolam

New formulations for addition to EMLc:
Midazolam injection 1mg/ml and 5mg/ml
Diazepam rectal tubes 2.5mg, 5mg and 10mg

- Benzodiazepines are considered the mainstay of pharmacological therapy for acute anxiety in adults and children, although evidence is based largely on expert opinion.

- Good quality evidence to support the role of benzodiazepines in the treatment of anxiety associated with terminal illness is limited.

- No studies comparing the safety and efficacy of one benzodiazepine over another were identified. The choice of benzodiazepines for inclusion in the EMLc for the management of acute anxiety in palliative care is therefore determined by availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.

- Diazepam is already included in EMLc for pre operative sedation and as an anticonvulsant for status epilepticus. Diazepam is appropriate for oral administration and has a relatively long half life appropriate for twice daily dosing

- Midazolam can be administered subcutaneously and can be administered as a continuous infusion with other medication for symptom management when the enteral route is no longer available. Midazolam can also be administered via the buccal route with rapid onset and ease of administration. There is evidence to support the safety of administration of midazolam via the buccal route in children.

SUMMARY OF MEDICINE RECOMMENDATIONS FOR INCLUSION IN EMLc FOR PALLIATIVE CARE				
DRUG	**CURRENTLY INCLUDED IN EMLc (or EML)**	**POTENTIAL ROLE(S) IN PALLIATIVE CARE**	**ADDITIONAL DOSAGE FORMS FOR INCLUSION**	**LICENSED STATUS IN UK, USA, AUSTRALIA**
AMITRIPTYLINE	**Antidepressant** (EML) 25mg oral tablets (EML)	**Adjunct in pain - neuropathic** **Depression**	Oral tablets 10mg	Enuresis - >5-6 years in Australia and UK Depression - >16 years in UK, 12 years in USA and Australia NOT licensed for treatment of neuropathic pain in children
CARBAMAZEPINE	**Anticonvulsant** (oral liquid 100mg/5ml; oral tablets 100mg, 200mg; oral chewable tablets 100mg, 200mg)	**Adjunct in pain - neuropathic** **Seizures**	None	Epilepsy – all ages
CODEINE	**Analgesic** (oral tablet 15mg, 30mg in EML)	**Pain**	Oral syrup BP 25mg/5ml	Pain from 1 year of age
CYCLIZINE	**No**	**Nausea and vomiting**	Oral tablets 50mg; injection 50mg/ml	Nausea and vomiting: from 6 years in UK and Australia
DEXAMETHASONE	**Anti-allergy / anaphylaxis** (injection 4mg/ml)	**Adjunct in pain** **Antiemetic** **Anorexia** **Fatigue** **Raised ICP**	Oral tablets 2mg	Various indications – all ages
DIAZEPAM	**Pre-op sedation; anticonvulsant** (injection 5mg/ml; oral tablets 5mg)	**Anxiety** **Anxiety associated with dyspnoea** **Adjunct in pain – muscle spasm**	Rectal tubes (2.5mg, 5mg, 10mg)	Anxiety/ agitation; muscle spasm – all ages for oral and injection
DOCUSATE SODIUM	**No**	**Constipation**	Oral capsules 100mg; oral solution	Constipation: UK from 6 months, USA from 2 years and Australia from 3 years

SUMMARY OF MEDICINE RECOMMENDATIONS FOR INCLUSION IN EMLc FOR PALLIATIVE CARE				
DRUG	**CURRENTLY INCLUDED IN EMLc (or EML)**	**POTENTIAL ROLE(S) IN PALLIATIVE CARE**	**ADDITIONAL DOSAGE FORMS FOR INCLUSION**	**LICENSED STATUS IN UK, USA, AUSTRALIA**
			50mg/5ml	
FLUOXETINE	**Anti-depressant** (>8 years) 20mg capsules	**Depression**	None	Depression > 8 years in UK and USA
HALOPERIDOL	**Anti-psychotic** Oral liquid 2mg/ml; tablets/capsules 0.5mg, 2mg, 5mg; injection 5mg/ml	**Agitation / delirium** **Antiemetic**	None	Behavioural disorders (e.g. hyperactivity, aggression, Tourettes, psychoses) – UK all ages (except injection); USA from 3 years; Australia from 5 years
HYOSCINE HYDROBROMIDE	**No**	**Excess respiratory secretions** **Nausea and vomiting**	Transdermal patches 1mg/72 hours; injection 400microgram/ml, 600microgram/ml	Nausea and vomiting: oral preparations from 3 years in UK; transdermal patches from 10 years in UK; Preoperative medication – injection: all ages in UK
IBUPROFEN	**Analgesic** (200mg, 400mg oral tablets)	**Pain**	Oral suspension 100mg/5ml	Pain and pyrexia from 3 months of age in UK, 6 months in USA and Australia
LEVOMEPROMAZINE	**No**	**Nausea and vomiting** **Confusion / delirium** **Adjunct in pain**	Oral tablets 25mg; injection 25mg/ml	Pain/distress in terminally ill; antiemetic: UK –lower age limit vague; does not appear to be widely available in USA or Australia
METOCLOPRAMIDE	**Anti-emetic** (oral liquid 5mg/5ml; oral tablet 10mg; injection 5mg/ml)	**Nausea and vomiting**	None	Nausea and vomiting: all ages
MIDAZOLAM	**No**	**Anxiety** **Agitation/delirium** **Sedation**	Injection 1mg/ml, 5mg/ml	Sedation – all ages

SUMMARY OF MEDICINE RECOMMENDATIONS FOR INCLUSION IN EMLc FOR PALLIATIVE CARE				
DRUG	**CURRENTLY INCLUDED IN EMLc (or EML)**	**POTENTIAL ROLE(S) IN PALLIATIVE CARE**	**ADDITIONAL DOSAGE FORMS FOR INCLUSION**	**LICENSED STATUS IN UK, USA, AUSTRALIA**
MORPHINE	**Analgesic** (oral liquid 10mg/5ml; immediate release oral tablet 10mg; s/r oral tablet 10mg, 30mg, 60mg; injection 10mg/ml)	**Pain** **Breathlessness / Dyspnoea**	Modified release granules (to mix with water) 20mg, 30mg, 60mg, 100mg, 200mg	Pain – from 1 year
PARACETAMOL	**Analgesic** (oral suspension 125mg/5ml; oral tablets 100mg to 500mg; suppository 100mg)	**Pain**	None	Pain and pyrexia from 3 months of age
SENNA	**Laxative** (EML) (Oral tablets 7.5mg)	**Constipation**	Oral syrup 7.5mg/5ml	Constipation: from 2 years

New medicines for addition to EMLc – MIDAZOLAM, DOCUSATE SODIUM, CYCLIZINE, LEVOMEPROMAZINE AND HYOSCINE HYDROBROMIDE

BACKGROUND

In the spring of 2007 a working party from the UK was asked by the World Health Organization (WHO) to prepare a summary of available evidence in support of the development of a WHO Essential Medicines List for palliative care for Children (EMLc: Palliative Care).

Following initial discussions a concept proposal was presented at the European Association for Palliative Care (EAPC) in June 2007 and the International Society for Paediatric Oncology (SIOP) in November 2007. Available evidence to support the development of the EMLc for children's palliative care was gathered and is summarized in this document.

This document is now being circulated for formal consultation. In addition to general responses, specific responses, using Delphi consensus building methodology is sought to support the development of the Essential Medicines List where evidence is weak or lacking.

Principles of World Health Organization essential medicines lists

- The concept of Essential Medicines in WHO is based on 3 criteria:
  1. Safety
  2. Efficacy
  3. Cost effectiveness
- The inclusion of medications in the WHO Model List of Medications does not include a formulary or instructions on dosages.
- The WHO Model List uses only formulations as a description of those which the WHO Expert Committee considers to be the most appropriate.
- The Formulary is published by WHO as a separate document and it is revised every two years, after the meeting and conclusions of the WHO Expert Committee on Essential Medicines takes place.

The WHO Essential Medicines List for Children: Palliative Care

DEFINITION OF PAEDIATRIC PALLIATIVE CARE [1]

- Palliative care for children is the active and total care of the child's body, mind and spirit, and also involves giving support to the family.
- It begins when illness is diagnosed and continues regardless of whether or not a child receives treatment directed at the disease
- Healthcare providers must evaluate and alleviate a child's physical, psychological and social distress.
- Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited
- It can be provided in tertiary care facilities, in community health services and even in children's homes

[1] EAPC Paediatric Palliative Care Taskforce. IMPaCCT: standards for paediatric palliative care in Europe. European Journal of Palliative Care 207; 14(3): 109-114

Life limiting illness is defined as a condition where premature death is usual, for example, HIV/AIDS

Life threatening illness is one where there is a high probability of premature death due to severe illness but there is also a chance of long term survival to adulthood. For example children receiving cancer treatment or admitted to intensive care after acute injury.

AIM OF THE EMLC PALLIATIVE CARE

The aim of the EMLc Palliative Care is to promote access to appropriate medicines for pharmacological management of symptoms in children with life threatening and life limiting (Life shortening) conditions including:

- Malignancy
- HIV/ AIDS
- Non malignant life limiting (life shortening) conditions

Optimum management of pain and other symptoms is essential at all times from diagnosis to end of life. Pain and symptom management should be provided in parallel to active treatment aimed at cure or prolonging survival not just as an alternative to active treatment at the end of life.

The aim of the EMLc Palliative Care is not to provide a comprehensive list of medicines that may be desirable for optimum management of distressing symptoms. But rather a list of the ABSOLUTE ESSENTIAL medicines required for the minimal acceptable standard for the care of critically ill and dying children.

EMLc Palliative Care prioritizes medicines for pharmacological management of the most important symptoms taking into account

- Most common causes of death in childhood in resource limited and resource rich countries
- Prevalence of symptoms within each diagnostic group
- Suffering attributable to individual symptoms
- Appropriateness of pharmacological management for individual symptoms
- Availability of appropriate pharmacological options for management of individual symptoms from within the existing list of medicines in the WHO EMLc
- Evidence of efficacy of pharmacological agent
- In the absence of comparative efficacy evidence between pharmacological agents, choice of agent to be based on safety, available formulations (most appropriate, least invasive route should be used) and cost effectiveness.

OBJECTIVES

- To identify the most important symptoms for paediatric palliative care
- To identify appropriate pharmacological approaches for management of individual symptoms
- To determine effectiveness and safety of identified pharmacological approaches

METHODS

Identification of the most important symptoms for paediatric palliative care

Worldwide childhood mortality national data was identified through internet searching of relevant websites and databases:

- World Health Organisation Mortality Database (http:///who.int/healthinfo/morttables/en/index.html)
- Demographic and Health Surveys (http://www.measuredhs.com/)
- UNICEF (http://wwww.childinfo.org)

Representative data was extracted to identify the most common causes of death from life threatening and life limiting conditions in infancy, childhood and adolescence for individuals aged 0 – 24 years during the last 10 years (1997-2007). Due to time constraints it was not possible to extract and process detailed data for all countries of the world. Instead a representative sample of data from resource rich and resource limited settings was extracted to support the development of the EMLc taking into account estimated coverage of the data and estimated completeness of the data.

Prospective studies, using validated self report tools augmented by parental report when self report was not possible, were sought to identify incidence, prevalence and suffering from specific symptoms in children and young adults aged 0 – 24 years, with life threatening and life limiting conditions. The following search strategy was utilized:

- MEDLINE (1966 – May 2008)
- EMBASE (1980 – May 2008)
- Hand searching of the references included in studies/papers identified from above
- Hand searching of targeted sources – this included a number of specialist palliative care journals (Journal of Clinical Oncology, J Pain and Symptom Management, Journal of Hospice and Palliative Nursing, Journal of Palliative Care, Palliative Medicine, Supportive Care in Cancer, European Journal of Palliative Care, American Journal of Hospice and Palliative Care) and resources

Where insufficient information was available from prospective studies using validated self report tools further information was gathered from retrospective studies.

Where direct comparison of identified studies was possible; patients within the same diagnostic group comparable methodology; the series were combined. Where this was not possible the data was summarized as individual or comparative data.

Pharmacological Management of Identified Symptoms

Following identification of the most prevalent and distressing symptoms a further literature search was undertaken to identify evidence to support the pharmacological management of these symptoms. Meta-analyses, systematic reviews or good quality randomised controlled trials specific to the pharmacological management of the identified symptom in paediatric palliative care were sought using the following search strategy:

- Evidence Based Reviews (Cochrane Library, DARE, HTA Database, NHS EED, ReFer)

- Evidence Based Guidelines (CKS incorporating Prodigy, SIGN, National Library of Guidelines, NICE Guidance, Protocols and Care Pathways)
- MEDLINE (1966 – March 2008)
- EMBASE (1980 – March 2008)
- Clinical queries on Pubmed (more general search strategy to identify any further systematic reviews or randomised controlled trials specific to the symptom but not necessarily palliative care)
- Hand searching of the references included in studies/papers identified from above
- Hand searching of targeted sources – this included a number of specialist palliative care journals (Journal of Clinical Oncology, J Pain and Symptom Management, Journal of Hospice and Palliative Nursing, Journal of Palliative Care, Palliative Medicine, Supportive Care in Cancer, European Journal of Palliative Care, American Journal of Hospice and Palliative Care) and resources (eg Twycross and Wilcock Palliative Care Formulary and Symptom Management in Advanced Cancer; BNFc)

Randomised, placebo controlled trials in the terminally ill (and especially in children) are logistically and ethically difficult to conduct, particularly during the last weeks and days of life. Consequently, the evidence base for pharmacological management of symptoms in palliative care is very weak. There is a paucity of data from well designed and clearly described studies and management of symptoms is largely based on expert opinion rather than evidence.

Given the lack of good quality evidence we also reviewed evidence of weaker quality such as prospective open studies, case series or retrospective reviews. In addition, expert opinion from specialists and specialist resources was considered.

The symptoms identified in the initial part of this review could also occur in other situations within the general paediatric population. It is likely that children in the palliative setting respond to pharmacological management of these symptoms in a similar way to children not in terminal phase. Consequently, in the absence of any other evidence, we also considered the evidence for pharmacological management of these symptoms in other children and included the evidence of safety and efficacy of drug treatment from any identified systematic reviews.

Each symptom was presented in a monograph with supporting references. The levels of evidence included in the reference tablets at the end of each symptom monograph are based on the SIGN (appendix 1) grading system. The strongest evidence (1++) is from high quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias. The weakest evidence (4) is evidence from expert opinion and general review articles.

RESULTS

Identification of the most important symptoms for paediatric palliative care

Recommendations
Management of the following symptoms and symptom clusters should be considered a priority for WHO EMLc Palliative Care ▪ Fatigue and weakness ▪ Pain ▪ Anorexia and weight loss ▪ Agitation and delirium ▪ Dyspnoea ▪ Nausea and vomiting ▪ Constipation ▪ Sadness or depression ▪ Excess respiratory tract secretions ▪ Anxiety

Summary of available evidence

EPIDEMIOLOGY

Accurate figures for the prevalence and mortality from life threatening and life limiting (life shortening) conditions in children are not available worldwide. In particular mortality from diseases in childhood is likely to be significantly under-reported in certain resource-limited settings [2].

Although global childhood mortality in the under-5 age group has decreased over the last 25 years the slowest reductions have been in Sub-Saharan Africa[3]. The decline in childhood mortality is due largely to improvements in infectious diseases associated with better sanitation, improved nutrition and public health. The prevalence of deaths due to life threatening and life limiting conditions relevant to paediatric palliative care is therefore increasing.

The most common cause of death in resource-limited countries is HIV/AIDS [4]. Worldwide mortality from HIV/AIDS in children under 15 years in 2007 has been estimated at 290,000 (270,00 – 320,000)

The most common cause of death, after trauma, in children aged 5 to 15 years in resource-rich countries is malignancy [5]. The annual incidence of malignancy in children aged 0 – 15 years is an estimated 16 000 worldwide.

Although up to 75% of childhood cancer can now be cured, most children with cancer in resource limited settings, and 80% of children worldwide will never be offered any active treatment and will therefore die from their malignancy. Few children in resource-limited settings and many children in resource-rich settings will have access to specialist palliative

[2] Manesh AO, Sheldon TA, Pickett KE, Carr-Hill R. Accuracy of childhood morbidity data in demographic and health services. Int J EPidemiol 2008; 37(1): 194-200
[3] Murray CJ, Laakso T, Shiuya et al. Can we achieve millennium development goal 4? New analysis of country trends and forcasts of under-5 mortality to 2015
[4] Http://www.childinfo.org/hiv_aids.html accessed 10/6/08
[5] WHO Mortality Database http://www.who.int/healthinfo/cod/en/index/html accessed 10/6/08

care. Therefore addressing symptoms identified as being prevalent in HIV/AIDS and malignancy would appear to be the priority for palliative care symptom management worldwide.

SYMPTOMS

No high quality prospective studies of symptoms and associated distress, using validated reporting tools, in children receiving palliative care were identified. Available evidence comprised almost exclusively retrospective case-note reviews, retrospective interviews from staff and studies of bereaved parents. One prospective study using reports from professionals was identified. Analysis of available evidence suggested 10 key symptoms and symptom clusters that should be considered a priority for EMLc palliative care.

Most frequently reported symptoms and attributable suffering in childhood malignancy [6, 7, 8, 9, 10, 11]

Rank	Reported symptoms	%	Reported suffering	%
1	Weakness	91	Fatigue	80
2	Fatigue	88	Lack of mobility	76
3	Pain	86	Pain	69
4	Poor appetite	84	Poor appetite	61
5	Weight loss	67	Dyspnoea	48
6	Agitation	63	Difficulty swallowing	44
7	Lack of mobility	62	Anxiety	36
8	Dyspnoea	57	Difficulty with speech	34
9	Nausea and vomiting	56	Problems with micturition	32
10	Constipation	52	Paralysis	29
11	Sadness or depression	53	Nausea and vomiting	23
12	Drowsiness	46	Constipation or diarrhoea	20
13	Difficulty with speech	42		
14	Headache	40		
15	Excess secretions	40		
16	Anaemia	39		
17	Pressure area problems	38		
18	Anxiety	36		

[6] Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. New England Journal of Medicine 2000; 342: 326-33

[7] Theunissen JMJ, Hoogerbrugge PM, van Achterberg T. et al. Symptoms in the palliative phase of children with cancer 2007. Paediatric Blood and Cancer; 49: 160-165.

[8] McCallum D, Byrne P, Bruera E. How children die in hospital. J Pain Symptom Manage 2000; 20(6): 417-423

[9] Goldman A, Hewitt M, Collins GS et al. Symptoms in children/young people with progressive malignant disease: United Kingdom Children's Cancer Study Group/ Paediatric Oncology Nurses Forum survey. Pediatrics 2006; 117(6): e1179-86

[10] Jalmsell L, Kreicbergs U, Onelöv E et al. Symptoms affecting children with malignancies during the last month of life: a nationwide follow-up. Pediatrics 2006; 117 (4): 1314-20

[11] Hongo T, Watanabe C, Okada S et al. Analysis of the circumstances at the end of life in children with cancer: symptoms, suffering and acceptance. Pediatrics International 2003; 45: 60-64

Incidence of symptoms in children with HIV/AIDs children [12] n = 73		
Symptom	**n**	**%**
Weight loss	80	84.2
Fever	53	55.8
Sores in mouth	48	50.5
Cough	47	49.5
Poor appetite	46	48.4
Diarrhoea	38	40
Pain	31	32.6
Vomting	22	23.2
Ear discharge	18	18.9
Difficulty breathing	11	11.6
Skin rash/changes	10	10.5

Most frequently reported symptoms in dying children: mixed cohort studies including cancer, Cerebral palsy, metabolic conditions and congenital abnormalities			
Rank	**Carter [13] n = 105**	**Drake[14] n = 30**	**Hunt [15] n = 30**
1	Dyspnoea	Fatigue	Pain
2	Seizures/ convulsions	Sedation/drowsiness	Sore mouth
3	[Pain]	Skin problems	Dyspnoea
4	Vomiting	Pain	Feeding difficulty
5	Anxiety/agitation	Anxiety/agitation	Problems with micturition
6	Terminal agitation	Swelling of arms or legs	Vomiting
7	Fatigue	Dyspnoea	Poor appetite
8		Cough	Diarrhoea
9		Poor concentration	Seizures/ convulsions
10		Problems with micturition	Difficulty swallowing

Most frequently reported symptoms in children dying from conditions other than cancer n=8 [8]		
Symptom	**Number of affected children**	**%**
Diarrhoea	1	12.5
Pain	3	37.5
Vomiting	1	12.5
Difficulty breathing	4	50
Feeding difficulty	6	75
Decreased consciousness	3	37.5

[12] Lavy V 2007 Presenting symptoms and signs in children referred for palliative care in Malawi. Palliative Medicine 2007 Jun;21(4):333-9.
[13] Carter B, Howenstein M, Gilmer M-J et al. Circumstances surrounding the deaths of hospitalised children: Opportunities for Pediatric Palliative Care. Pediatrics 2004 Sep;114(3):e361-6.
[14] Drake R, Frost J and Collins JJ. The symptoms of dying children. J Pain Symptom Manage 2003; 594-603
[15] Hunt A. A survey of signs, symptoms and symptom control in 30 terminally ill children. Dev Med Ped Neurol 1990; 32: 341-6

IDENTIFICATION OF MOST IMPORTANT SYMPTOMS FOR PAEDIATRIC PALLIATIVE CARE: SUMMARY OF EVIDENCE					
#	**Reference**	**Study type**	**Subjects**	**Results**	**Grade of evidence**
6	Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. New England Journal of Medicine 2000; 342: 326-33	Interviews of bereaved parents who had lost a child to cancer a mean of 3.1 years after the death; supplemented by casenote review	n = 103	89% of children suffered "a lot" or "a great deal" from 1 or more symptoms in the last month of life; most commonly pain, fatigue and dyspnoea	Not applicable
7	Theunissen JMJ, Hoogerbrugge PM, van Achterberg T. et al. Symptoms in the palliative phase of children with cancer 2007. Paediatric Blood and Cancer; 49: 160-165.				Not applicable
8	McCallum D, Byrne P, Bruera E. How children die in hospital. J Pain Symptom Manage 2000; 20(6): 417-423	Retrospective review of medical and nursing notes of last 7 days of life for children dying in hospital following	n = 17 not ventilated at time of death; of these 9 with cancer		Not applicable
9	Goldman A, Hewitt M, Collins GS et al. Symptoms in children/young people with progressive malignant disease: United Kingdom Children's Cancer Study Group/ Paediatric Oncology Nurses Forum survey. Pediatrics 2006; 117(6): e1179-86	Questionnaire survey of professionals caring children in UK cancer centres. Children were enrolled in the study when curative treatment was no longer available and professionals completed monthly questionnaires until the child died	164 children aged 4 months – 19 years	Most common symptoms were pain, anorexia, weight loss, fatigue & weakness. Symptom prevalence increased at study entry to the last month of life. Symptoms that responded least well to treatment included weakness, poor mobility, anorexia and difficulty with swallowing and speech	Not applicable
10	Jalmsell L, Kreicbergs U, Onelöv E et al. Symptoms affecting children with malignancies during the last month of life: a nationwide follow-up. Pediatrics 2006; 117 (4): 1314-20	Postal questionnaire study of symptoms in the last month of life as reported by bereaved parents 4 – 9 years after the death of their child from cancer	n = 449 parents (some from the same family)	Fatigue, reduced mobility pain and decreased appetite were most frequently reported with high or moderate impact on quality of life in the child's last month of life	Not applicable
11	Hongo T, Watanabe C, Okada S et al. Analysis of the circumstances at the end of life in children with cancer: symptoms, suffering and acceptance. Pediatrics International 2003; 45: 60-64	Retrospective casenote review of children with cancer in Japan	28 children		Not applicable
12	Lavy V 2007 Presenting symptoms and signs in children referred for palliative care in Malawi Palliative Medicine 2007 Jun;21(4):333-9.	Direct questioning of families of parents presenting to a hospital in Malawi supplemented by physical examination of the child	n=95; children aged 4 months to 16 years; 73 with HIV/AIDs; 16 with cancer	**Most common symptoms in theHIV/AIDs group were weight loss fever sore mouth and cough. Symptom reporting was enhanced by direct questioning and examination**	Not applicable
13	Carter B, Howenstein M, Gilmer M-J et al. Circumstances surrounding the deaths of hospitalised children: Opportunities for Pediatric Palliative Care. Pediatrics 2004 Sep;114(3):e361-6.	Retrospective review of medical notes for last 72 hours of life for children dying in neonatal intensive care, pediatric critical care and general pediatric unit	n = 105; 10% with malignancy	Presence of symptoms other than pain was infrequently documented; most prevalent symptoms in the last 72 hours of life were prolonged crying – interpreted as pain, dyspnoea and seizures or convulsions	Not applicable
14	Drake R, Frost J and Collins JJ. The symptoms of dying children. J Pain Symptom Manage 2003; 594-603	Retrospective review of medical and nursing notes for the last week of life for children dying in hospital	n=30; 18 with malignancy	Lack of energy, drowsiness, skin changes, irritability, pain swelling of limbs, cough and dyspnoea overall most frequently reported symptoms	Not applicable
16	Brook L, Vickers J and Osbourne C. Paediatric palliative care drug boxes: facilitating safe and effective symptom management at home at the end of life. Arch Dis Child 2007; Supp 1: A58	Retrospective review of prescription and drug administration sheets and casenotes for the last 2 weeks of life in a single centre in the UK	69 children; 50 with cancer 19 with other life limiting conditions	78% of reported symptoms were controlled with a combination of one or more of 6 "essential drugs" administered by the intravenous or subcutaneous route. However fatigue, weakness, anorexia and weight loss were not specifically assessed	Not applicable

PHARMACOLOGICAL MANAGEMENT OF IDENTIFIED SYMPTOMS

Principles of symptom management

- Pharmacological management is only one aspect of symptom management in palliative care and in addition attention to social psychological and spiritual distress is essential
- A multidisciplinary approach is essential
- Regular assessment and regular review
- Assessment of the severity of identified symptoms and their impact on quality of life
- Identification and treatment of any reversible underlying cause where appropriate
- Medication in an appropriate dose titrated to the needs of the child
- Regular medication to ensure that symptoms remain controlled
- In addition "as required" medication should be available at all times to ensure that symptoms can continue to be controlled as the child's condition deteriorates or new symptoms develop
- Administration of medication by the most appropriate route
- This is the least invasive route and is normally the enteral route
    - Where the enteral route is not available the least painful route should be used
    - The subcutaneous route is used in preference to the intravenous route unless the child has long term central venous access
- Where medication is required regularly, use of sustained release preparations is recommended to reduce dosing frequency, improve concordance and reduce fluctuations of symptoms at "end of dose".
- If the enteral route is no longer available delivery of a combination of medicines via a continuous subcutaneous (or intravenous if the child has long term central venous access) infusion is recommended.

Essential medicines

Evidence for use of an "essential medicines list" for management of symptoms at end of life in children

- A retrospective casenote review [16] of a cohort of children with malignant (n=50) and non malignant (n=19) diagnoses suggested that approximately 78% of reported symptoms were controlled with a combination of one or more of 6 "essential drugs" administered by the intravenous or subcutaneous route.
- However fatigue, weakness, anorexia and weight loss were not specifically assessed

[16] Brook L, Vickers J and Osbourne C. Paediatric palliative care drug boxes: facilitating safe and effective symptom management at home at the end of life. Arch Dis Child 2007; Supp 1: A58

"6 essential medicines" administered by continuous subcutaneous or intravenous infusion to successfully control 78% symptoms in a mixed cohort of dying children (n=69) [16]	
Drug	**Indication**
Morphine (or alternative strong opioid)	Pain Breathlessness
Midazolam	Anxiety Seizures Terminal agitation
Cyclizine	Nausea and vomiting
Haloperidol	Nausea and vomiting if cyclizine alone ineffective
Levomepromazine	Nausea and vomiting if cylizine with haloperidol ineffective
Hyoscine hydrobromide	Respiratory tract secretions (death rattle)

Where this alone is inadequate evidence for use of an "essential medicines list" for management of symptoms at end of life in adults

- The EAPC and WHO has compiled an essential medicines list for palliative care in adults [17]
- However this list was compiled on the basis of expert opinion alone without direct recourse to a systematic review of the supporting literature
- The EML for adult palliative care includes 34 medicines of which 14 are already included in the WHO EML for adults. However there is ongoing discussion regarding the validity of the recommendations without reference to the supporting literature and the justification for inclusion of several drugs from the same pharmacological class.

Fatigue and weakness

NO PHARMACOLOGICAL AGENT RECOMMENDED

DEFINITION

Fatigue is defined as a subjective feeling of tiredness, weakness or lack of energy.

SCOPE

- Fatigue is a complex multidimensional symptom comprising physical cognitive and emotional aspects
- Fatigue at the end of life may have a protective role. Treatment of fatigue may not be appropriate if this symptoms is not having a direct impact on quality of life
- Management of fatigue comprises identification and, if appropriate, treatment of possible underlying cause(s) and the use of pharmacological and non pharmacological management of the fatigue itself
- Here we consider only pharmacological management of fatigue

OVERVIEW OF MANAGEMENT OPTIONS

CLASSES OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

[17] De Lima L, Krakauer EI, Lorenz K et al. Ensuring palliative medicine availability: the development of the IAHPC list of essential medicines for palliative care. J Pain Symptom Manage 2007; 33(5): 521-6

- Psychostimulants
- Corticosteroids (dexamethasone)

PSYCHOSTIMULANTS (METHYLPHENIDATE) IN THE MANAGEMENT OF FATIGUE AND WEAKNESS

Recommendations
Relatively few studies have been conducted to evaluate the effectiveness of psychostimulants in adults for fatigue in palliative care [1]
Open-label studies have shown methylphenidate to be effective in adults with cancer-related fatigue but a single double-blind study failed to find any effect significantly different to placebo [1]
Double-blind trial in adult patients with HIV-related fatigue showed a beneficial effect of methylphenidate over placebo [2]
No evidence of use in children for treatment of fatigue in palliative care

Evidence for management of this symptom with this drug in children
No evidence has been identified to support the use of methylphenidate in the management of fatigue and weakness associated with palliative care in children

Where this alone is insufficient: evidence for management of this symptom in adults
- Open-label trials showed methylphenidate improved fatigue in adult patients with cancer
- A single randomized controlled trial of methylphenidate failed to show any significant improvement in fatigue compared with placebo
- Side effects of methylphenidate may be dose limiting and include nervousness jitteriness, agitation, cardiac arrthymia and tachycardia

Additional supporting information for this drug
No additional information included as methylphenidate unlikely to be included in the EMLc for palliative care.

CORTICOSTEROIDS IN THE MANAGEMENT OF FATIGUE AND WEAKNESS IN PALLIATIVE CARE

Recommendations
Very few studies have been conducted to evaluate the effectiveness of corticosteroids in fatigue in adults [5]
Clinical trials with corticosteroids do not use improvement in fatigue as a primary outcome. Improvements in pain and quality of life with corticosteroids had a resultant positive effect on fatigue with a reduction in severity of this symptom [5]
No trials to compare effectiveness of one corticosteroid with another [5]
Expert opinion describes short-term use of dexamethasone in adults [6]
No evidence of use in children for treatment of fatigue in palliative care

Evidence for management of this symptom with this drug in children
No evidence has been identified to support the use of corticosteroids in the management of fatigue associated with palliative care in children.

Where this alone is insufficient: evidence for management of this symptom in adults
- Although expert opinion supports the use of corticosteroids for the management of a variety of symptoms, including fatigue, in palliative care the evidence is weak.
- Two randomized controlled trials of corticosteroids have suggested that these drugs may have a beneficial effect on fatigue. However improvement in fatigue was not a primary outcome for these studies.

- One randomized clinical trial suggests that treatment of anorexia/ cachexia with megestrol acetate may also result in secondary improvement in fatigue.

PSYCHOSTIMULANTS (Methylphenidate) IN THE MANAGEMENT OF FATIGUE AND WEAKNESS IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
1	Carroll JK et al. Pharmacologic treatment of cancer-related fatigue. The Oncologist, 2007; 12(Suppl 1): 43-52	Systematic review to identify and analyse clinical trials in the US, Canada and Europe that assessed pharmacological interventions for cancer-related fatigue.	32 clinical trials identified, 19 prospective open trials and 13 RCTs. For methylphenidate 7 open trials and 1 randomised controlled trial identified	▪ Open-label trials showed methylphenidate improved fatigue in adult patients with cancer ▪ Single randomised controlled trial of methylphenidate failed to show any significant improvement in fatigue compared with placebo	Given the relatively few studies conducted to confirm efficacy, the potential adverse effects of these agents must be considered before use	1+
2	Radbruch L et al. Fatigue in palliative care patients - an EAPC approach. Palliative Med 2008; 22: 13-32				No additional studies identified to those included in above systematic review	
3	Breithart W et al. A randomised, double-blind placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with HIV disease. Arch Intern Med, 2001; 161: 411-420	Double-blind randomised, placebo controlled trial	144 adult patients with HIV disease and persistent fatigue, randomised to treatment with methylphenidate, pemoline or placebo. 109 patients completed the 6 week trial	▪ 15 patients (41%) on methylphenidate and 12 patients (36%) on pemoline demonstrated clinically significant improvement compared with placebo (15%)		1+
4	Regnard and Hockley. A guide to symptom relief in palliative care. 5th Edition	Expert opinion			Psychostimulants such as methylphenidate are occasionally used to achieve a rapid effect when this is needed for a special event, but anxiety, anorexia and insomnia can occur.	4

CORTICOSTEROIDS IN THE MANAGEMENT OF FATIGUE AND WEAKNESS IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of evidence**
5	Carroll JK et al. Pharmacologic treatment of cancer-related fatigue. The Oncologist, 2007; 12(Suppl 1): 43-52	Systematic review to identify and analyse clinical trials in the US, Canada and Europe that assessed pharmacological interventions for cancer-related fatigue.	32 clinical trials identified, 19 prospective open trials and 13 RCTs. 2 clinical trials of corticosteroids and one trial of anabolic steroids identified. 2 studies were randomised, double-blind crossover studies	▪ Studies reported improvements in symptoms, especially pain and showed improved quality of life and reduced fatigue ▪ Single agent used in each trial, 1 each of prednisolone, methylprednisolone and megestrol acetate)	None of the 3 reported clinical trials of corticosteroids had improvement in fatigue as a primary outcome measure Sample sizes small (37-84/study) Studies were of short duration	1+
6	Radbruch L et al. Fatigue in palliative care patients - an EAPC approach. Palliative Med 2008; 22: 13-32	Report from a consensus conference			No additional studies identified to those included in above systematic review	
7	Regnard and Hockley. A guide to symptom relief in palliative care. 5th Edition	Expert opinion			In fatigue related to advanced disease without a clear cause, there is little evidence that drugs have any long-term benefit. Dexamethasone 2-4mg daily can give a short-term improvement for up to 4 weeks	4

Pain

Recommendations for Inclusion: PARACETAMOL, IBUPROFEN, CODEINE, MORPHINE, AMITRIPTYLINE, CARBAMAZEPINE, and DEXAMETHASONE

No new medicines for addition to EMLc as all of the above are currently included

New formulations for addition to EMLc:
Ibuprofen oral suspension 100mg/5ml
Codeine oral syrup 25mg/5ml
Morphine sulphate modified release granules 20mg, 30mg, 60mg, 100mg and 200mg
Amitriptyline oral tablets 10mg
Dexamethasone oral tablets 2mg

DEFINITION

- "Pain is whatever the patient says hurts"
- Pain is an unpleasant sensor and emotional experience associated with actual or potential tissue damage or described in terms of such damage (International Association for the Study of Pain 2007)

SCOPE

- Pain is multidimensional having physical, psychological, social and spiritual aspects; all these may need addressing. Here we only consider pharmacological management.
- The pharmacological management of pain is appropriate at all times including when active treatment aimed at cure or prolongation of life is being considered.
- Management of pain should not be deferred until the underlying cause of the pain has been identified but treatment of pain and identification and if appropriate treatment of the underlying cause should be undertaken simultaneously.

OVERVIEW OF MANAGEMENT OPTIONS

- Pain should be managed according to the principles of the WHO analgesic ladder
- Pain is classified as mild, moderate or severe and appropriate analgesia is chosen according to the severity of the pain
    - Step 1: mild pain, paracetamol or a non-steroidal anti-inflammatory drug (NSAID)
    - Step 2: mild to moderate pain, codeine (with paracetamol or NSAID)
    - Step 3: moderate to severe pain, morphine.
- At each stage, appropriate adjuvant therapy should be considered e.g.
    - Neuropathic pain – anticonvulsants and/or antidepressants
    - Bony pain – NSAIDs
    - Muscle spasm - Antispasmodics
- Dose of analgesia should always be adjusted as the pain severity alters.
- If pain severity increases and is not controlled on a given step, move upwards to the next step of the ladder. A different analgesic of the same potency should not be prescribed.

ANALGESICS FOR PAIN

CLASSES OF DRUG THAT MAY BE APPROPRIATE FOR MANAGEMENT OF THIS SYMPTOM

- Paracetamol
- Non steroidal anti-inflammatory drugs
- Weak opioids
- Strong opioids

ANALGESICS IN THE MANAGEMENT OF PAIN IN PALLIATIVE CARE

Recommendations
Inclusion of paracetamol as an analgesic for the management of mild pain in paediatric palliative care
Inclusion of ibuprofen as an analgesic for management of mild pain in paediatric palliative care
Inclusion of codeine as an analgesic of choice for management of mild moderate pain in paediatric palliative care
Inclusion of morphine as the single strong opioid of choice for management of moderate to severe pain in paediatric palliative care to ensure worldwide availability and use

Paracetamol

No further work done on paracetamol.

- Paracetamol is included in the EMLc as an analgesic and anti-migraine agent. Paracetamol has proven efficacy as an analgesic in children and has an excellent safety profile when administered at the licensed dosage.
- The formulations currently included in the EMLc are an oral suspension 125mg/5ml, oral tablets 100mg to 500mg and suppository 100mg enabling paracetamol to be administered by the oral and rectal routes.
- Paracetamol is licensed as an analgesic and antipyretic from 3 months of age.

Ibuprofen

No further work done on ibuprofen.

- Ibuprofen is included in the EMLc as an analgesic and anti-migraine agent. Ibuprofen has proven efficacy as an analgesic in children and has minimal adverse effects when administered at the licensed dosage.
- The formulations currently included in the EMLc are oral tablets 200mg and 400mg. Ibuprofen is also widely available as an oral suspension 100mg/5ml and this would be a useful addition for those children unable to swallow tablets.
- Ibuprofen is licensed as an analgesic and antipyretic from 3 months of age in the UK (6 months in USA and Australia).

Codeine

No further work done on codeine.

- Codeine is included in the EMLc as an analgesic.
- Codeine has proven efficacy as an analgesic in children. As an opioid, codeine does have the potential to cause adverse effects such as constipation but these can generally be managed.
- The formulation currently included in the EMLc is oral tablet 15mg (with oral tablets 30mg included on the adult list). Codeine phosphate is also widely available as an oral syrup 25mg/5ml or oral linctus 15mg/5ml and the inclusion of a liquid oral preparation would be a valuable addition to the EMLc for those children unable to swallow tablets.

- Codeine is licensed as an analgesic from 1 year of age; in the UK the tablets are not licensed for children.

Morphine

Limited work done on morphine. Morphine is widely accepted as the strong opioid of choice in moderate to severe pain. This is confirmed by a number of consensus guidelines (see below). [8] [9] [10] [11][12]

- Morphine is included in the EMLc as an analgesic and as pre-operative medication and sedation for a short-term procedure.
- Morphine has proven efficacy as an analgesic in children and has an important role in the control of moderate to severe pain in palliative care.
- Opioids may be underutilized often due to unsubstantiated fear by physicians, patients and their families of opioid addiction and tolerance.
- Additionally, the strict regulation and control of these agents in most countries may present prescription difficulties.
- Morphine is the most widely available strong opioid and given its proven efficacy, its use is recommended in moderate to severe pain in palliative care.
- The formulations currently included in the EMLc are injection 10mg/ml; oral liquid 10mg/5ml; immediate-release tablet 10mg; modified release tablet 10mg, 30mg, 60mg enabling morphine to be administered by parenteral or oral routes.
- The inclusion of both immediate release and sustained release oral preparations enables morphine to be successfully used in both acute and prolonged pain episodes.
- Inclusion of a modified release oral suspension would be a valuable addition for those children unable to swallow sustained release tablets.
- Morphine is licensed for use from 1 year of age.

ALTERNATIVE OPIOIDS CONSIDERED:

Transdermal fentanyl [14] [15] [16]

- Shown to be effective and is a possible alternative to morphine in the management of moderate to severe pain.
- This is a useful route of administration as an alternative to the oral or parenteral routes. Transdermal fentanyl is an option in case of adverse effects to morphine or in those with renal impairment.
- However, transdermal fentanyl patches are expensive and not widely available world-wide. The patches are licensed for use from 2 years of age.

Transmucosal fentanyl in breakthrough pain [13]

- A Cochrane systematic review has shown transmucosal fentanyl to be effective and an alternative to immediate release morphine in the management of breakthrough pain. However, this review included only 4 randomised controlled trials (393 participants) of which none included children.
- There is limited data on the use of transmucosal fentanyl in children, it is not widely available worldwide and is expensive.
- Transmucosal fentanyl lozenges are not licensed for use in children.

Oxycodone [18]

- Oxycodone is a possible alternative to morphine with a Cochrane systematic review indicating efficacy and tolerability similar (but NOT superior) to morphine.
- Oxycodone does not appear to offer any advantage over morphine as a first choice opioid analgesic.

- Oxycodone is not licensed for use less than 18 years of age in the UK, USA or Australia.

Hydromorphone [17]
- Hydromorphone is a possible alternative to morphine with a Cochrane systematic review showing hydromorphone to be a potent analgesic.
- However, the limited evidence available does not demonstrate any clinically significant difference between hydromorphone and morphine.
- Hydromorphone is licensed as an analgesic from 12 years of age in the UK and USA.

Diamorphine [25] [26] [27]
- Diamorphine has a useful role for administration by subcutaneous infusion due to greater solubility (compared with morphine) when fluid volume for parenteral administration is restricted.
- However, diamorphine is not widely used or available outside the UK.

Methadone [19] [20] [21] [22] [23] [24]
- There is some clinical experience of methadone in palliative care described in the literature and methadone may have a role in cases of intolerance to other strong opioids or those with morphine poorly responsive pain.
- Methadone is not however, considered a first line choice and its complex pharmacokinetic profile can make it a difficult drug to use.
- Methadone is not licensed for use in children or adults outside of substance dependent programmes.

CO-ANALGESICS FOR NEUROPATHIC PAIN

CLASSES OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

- Antidepressants
- Anticonvulsants
- Corticosteroids

ANTIDEPRESSANTS IN THE MANAGEMENT OF PAIN IN PALLIATIVE CARE

Recommendations
Tricyclic antidepressants are effective in the management of neuropathic pain in adults [28]
Amitriptyline is effective in the management of neuropathic pain in adults [28] [29]
Established clinical use and expert opinion suggest amitriptyline is of value in the management of neuropathic pain in paediatric palliative care [30] [31] [32]

Evidence for management of this symptom with this drug in children
No studies on use of amitriptyline in paediatric palliative care pain were identified. However, use in other types of chronic pain such as migraine is well established.

Where this alone is insufficient: evidence for management of this symptom in adults
- A Cochrane systematic review looking at the analgesic effectiveness and safety of antidepressants in neuropathic pain in adults confirmed the efficacy of tricyclic antidepressants with amitriptyline being the most commonly used.

- Further research is needed with regard to the newer types of antidepressants to assess their efficacy in neuropathic pain since these drugs are generally regarded as being better tolerated than tricyclic antidepressants.

Additional supporting information for this drug

- Amitriptyline is included in the EML (>12 years) as an antidepressant.
- The formulation currently included is oral tablet 25mg.
- Amitriptyline has several useful roles in children – for enuresis (licensed in UK and Australia from 5-6 years), as an antidepressant (licensed in the UK from 16 years and the USA from 12 years) as well as for chronic pain (unlicensed indication).
- Amitriptyline is widely available and cheap.
- There is considerable clinical experience in children, most notably in enuresis and its use in chronic pain such as migraine is well established.
- The low doses generally used in chronic pain should help to minimise potential adverse effects but these should be considered.
- Amitriptyline is also available as 10mg tablets and in the UK as an oral solution 25mg/5ml, 50mg/5ml and these preparations may be useful additions to the EMLc.

ANTICONVULSANTS IN THE MANAGEMENT OF PAIN IN PALLIATIVE CARE

Recommendations
Anticonvulsants may be effective in chronic pain syndromes in adults [33]
Anticonvulsants are not effective in acute pain [33]

CARBAMAZEPINE

Recommendations
Carbamazepine is effective in the treatment of neuropathic pain [34]
Established clinical use and expert opinion suggest carbamazepine is of value in the management of neuropathic pain in children [35] [36]

Evidence for management of this symptom with this drug in children

Use of carbamazepine in neuropathic pain in children is established but based largely on data extrapolated from adults and clinical experience rather than any high quality studies.

Where this alone is insufficient: evidence for management of this symptom in adults

- Like amitriptyline, carbamazepine has been a mainstay of therapy of neuropathic pain for many years.
- A systematic review confirms the efficacy of carbamazepine in neuropathic pain. However, of the 12 studies included, trigeminal neuralgia and diabetic neuropathy were the primary indications.
- There is still a need for high quality studies of the relative effectiveness of different anticonvulsants in chronic pain syndrome and for comparisons of other treatments such as antidepressants with anticonvulsants.
- Use of carbamazepine has been discouraged by emergence of newer compounds such as gabapentin that do not have the same need for monitoring and potential for drug interactions. However, although gabapentin has been shown to be effective in chronic pain, there is no data to suggest it is any more effective than carbamazepine as a first line choice.

Additional supporting information for this drug

- Carbamazepine is included in the EMLc as an anticonvulsant.
- The use of carbamazepine in the management of seizures is long established and carbamazepine is regarded as effective and relatively well tolerated.
- Carbamazepine is licensed in the UK, USA and Australia for the treatment of epilepsy in infants and children of all ages.
- Carbamazepine is cheap and widely available. The formulations currently included in the EMLc are an oral liquid 100mg/5ml, chewable oral tablets 100mg, 200mg and oral tablets 100mg and 200mg.
- Given that the use of anticonvulsants in chronic pain is established, carbamazepine offers an effective and more affordable alternative than gabapentin especially where economic resources are scarce.

GABAPENTIN

Recommendations
There is good evidence to show Gabapentin is effective in chronic pain in adults [37]
Gabapentin is not effective in acute pain [37]
Gabapentin in combination with a opioid may provide better relief of neuropathic pain than opioid alone [38] [39]
Established clinical use and expert opinion suggest gabapentin is of value in the management of neuropathic pain in children [41] [42]
Gabapentin has not been shown to be any more effective than carbamazepine, is less readily available and is more expensive

Evidence for management of this symptom with this drug in children

Evidence for use in children is extrapolated from adult data and from clinical experience and opinion.

Where this alone is insufficient: evidence for management of this symptom in adults

- There is good evidence from a high quality systematic review to confirm the efficacy of gabapentin in the management of neuropathic pain in adults.
- Gabapentin needs to be considered alongside other proven treatments such as carbamazepine and amitriptyline. These provide effective and more affordable alternatives where economic resources are scarce.
- Further high-quality studies required to assess the relative effectiveness of different anticonvulsants and to compare this group of drugs with the antidepressants.

Additional supporting information for this drug

- No additional work done on gabapentin.
- Although shown to be effective in chronic pain, gabapentin has not been shown to be any more effective than carbamazepine and is more expensive and not as readily available.
- Gabapentin is not currently included in the EMLc or the EML.

CORTICOSTEROIDS

DEXAMETHASONE

Recommendations
Although frequently used in the management of pain associated with terminal illness, there is little good quality evidence base
Corticosteroids have been shown to reduce pain in various situations. The major mode of action is likely to be anti-inflammatory but there is also a possible central analgesic effect [43] [44] [45]
Corticosteroids have many potential side effects and complications; response and adverse effects should be closely monitored and dexamethasone stopped if therapeutic response is inadequate

Evidence for management of this symptom with this drug in children
Evidence for use in children is extrapolated from adult data and from clinical experience and opinion.

Where this alone is insufficient: evidence for management of this symptom in adults
- Despite the little evidence base to support the use of corticosteroids in palliative care, they are generally regarded as having a number of potential roles and there is much clinical experience of corticosteroids in palliative care.
- Corticosteroids have been advocated for the relief of pain due to tumour compression and for emergency treatment of malignant spinal cord compression.
- Corticosteroids appear *to* reduce the headache of raised intracranial pressure by reduction in peritumour oedema
- Corticosteroids may not be effective in reducing pain where nerve compression is not an associated factor
- Although corticosteroids do have many potential side-effects and complications, general opinion from experts in palliative care is that the benefits of therapy in patients with advanced and terminal illness probably outweigh the risks of adverse effects.
- However, the lowest effective dose should be used and therapy discontinued if no benefit is obtained or any initial benefit is lost.
- Although dexamethasone appears to be the most commonly used corticosteroid in palliative care, the choice is largely arbitrary and the choice between dexamethasone and prednisolone likely to be determined by fashion, cost and availability.
- Although the full benefit may be short lived it can be difficult to reduce and stop corticosteroids given for this indication with increased risk of adverse effects including disturbance in appetite, mood and significant weight gain

Additional supporting information for this drug

DEXAMETHASONE
- Dexamethasone is included in the EMLc for use in allergy or anaphylaxis. The only preparation currently listed is the injection 4mg/ml.
- Dexamethasone is widely available in the UK, USA and Australia as oral tablets (0.5mg, 2mg) and these would be a valuable inclusion to the EMLc.
- Dexamethasone is also available as an oral solution which would also be a valuable inclusion. However, dexamethasone tablets readily dissolve in water so in those countries with an acceptable quality of water, dissolving tablets is a suitable alternative to an oral solution.

- Dexamethasone is licensed in the UK, USA and Australia for children of all ages for a variety of indications and there is wide clinical experience to confirm efficacy.
- There are a number of known potential adverse effects of corticosteroids and these must always be considered before dexamethasone is used.
- Dexamethasone has high glucocorticoid activity but insignificant mineralocorticoid effect and is particularly suitable for high dose therapy.
- The plasma half life of dexamethasone is 3.5-4.5 hours but as the effects outlast the significant plasma concentrations of steroids, the plasma half-life is of little relevance and the use of biological half life is more applicable. The biological half life of dexamethasone is 36-54 hours, therefore dexamethasone is especially suitable in conditions where continuous glucocorticoid action is desirable.
- The approximate equivalent anti-inflammatory doses 750microgram dexamethasone ~ 5mg prednisolone.

CO-ANALGESICS FOR BONY PAIN

NON-STEROIDAL ANTI-INFLAMMATORY AGENTS

- Ibuprofen (No further work done – see above)

Non-steroidal anti-inflammatory drugs (NSAIDs) have theoretical advantage in bone pain due to their peripheral anti-inflammatory effect. Their efficacy in reducing pain and opioid doses has been demonstrated although not specifically in patients with bony metastases or in children [54].

CO-ANALGESICS FOR MUSCLE SPASM

- Benzodiazpeines (skeletal muscle)
- Baclofen (skeletal muscle)
- Hyoscine butylbromide (smooth muscle)

No good evidence base was identified for any of these agents in palliative care as adjunct analgesics in pain associated with muscle spasm. However, diazepam is currently included in the EMLc for other indications and could be utilised as necessary.

MORPHINE IN THE MANAGEMENT OF MODERATE TO SEVERE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
8	WHO 1998	Consensus guideline			▪ Morphine regarded as opioid of first choice in the management of moderate and severe acute and chronic pain including that of palliative care	4
9	Hanks GW et al. Morphine and alternative opioids in cancer pain. European Working Group of the Research Network of the European Association for Palliative Care. British Journal of Cancer 2001; 84: 587-593	Consensus guidelines			▪ As above	4
10	Scottish Intercollegiate Guidelines Network 2007. Control of pain in patients with cancer	Consensus guidelines			▪ As above	4
11	CKS – Palliative Care – Pain 2007	Consensus guidelines			▪ As above	4
12	Wiffen PJ et al. Oral morphine for cancer pain. Cochrane Database of Systematic Reviews 2007	Systematic review	Systematic review of published randomised controlled trials of 10 or more participants (adults or children) looking at the efficacy of oral morphine in relieving pain	▪ No studies with children identified ▪ Oral preparation of morphine was compared with either placebo, an alternative presentation or an active control ▪ 54 studies (3749 participants) included ▪ Oral morphine, used at the correct dose for the individual, is effective in controlling pain	▪ The review had tried to compare the different brands of modified release preparations in terms of effectiveness. Although analysis confirmed the effectiveness of these preparations, it was not possible to demonstrate the superiority of one product over another either by brand or by length of time release	1++

FENTANYL IN THE MANAGEMENT OF MODERATE TO SEVERE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
13	Seppetella G et al. Opioids for the management of breakthrough (episodic) pain in cancer. Cochrane Database of Systematic Review 2006	Systematic review	Four randomised controlled trials of 393 participants in which opioids were used as rescue medication against an active or placebo comparator in patients with cancer pain	▪ Current approach is to use rescue medication at a dose proportional to the total daily opioid dose (usually oral morphine at 1/6th total daily dose) ▪ All 4 studies identified in this review concerned the use of oro-transmucosal fentanyl citrate ▪ When compared with placebo and morphine participants, OTFC gave lower pain intensity scores and higher pain relief scores at all time points	▪ Oral opioids generally have an onset of effect of 20-30 minutes which may not be ideal in acute situation ▪ The absorption pharmacokinetics of fentanyl from Actiq are a combination of rapid oromucosal absorption and slower gastrointestinal absorption of swallowed fentanyl. Approximately 25% of the total dose of Actiq is rapidly absorbed from the buccal mucosa. The remaining 75% of the dose is swallowed and slowly absorbed from the gastrointestinal tract. T_{max} is around 20 to 40 minutes after consumption of an Actiq unit (range 20 – 480 minutes).	1++
14	Zernikow B et al. Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. J Pain, 2007; 8(43): 187-207	Systematic review	11 observational studies in children and adolescents included. No paediatric randomised or controlled cohort studies	▪ Fentanyl transdermal is a useful option for chronic pain control in children ▪ No fundamental differences in the effect or profile of adverse effects compared with adults ▪ Fentanyl transdermal may be associated with less constipation when compared with morphine ▪ Younger patients tend to have a higher fentanyl requirement when referenced to body weight	▪ Not palliative care	2++
15	Clark AJ et al. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. Curr Med Res Opin 2004; 20(9): 1419-28	Pooled analysis conducted on datasets of published, open-label uncontrolled and randomised controlled studies	8 trials (1220 adult patients) with treatment duration of at least 28 days in which transdermal fentanyl was compared with sustained release morphine	▪ Both transdermal fentanyl and sustained release morphine effective in improving pain ▪ Transdermal fentanyl significantly more effective than sustained release morphine especially in those with non-cancer pain ▪ Transdermal fentanyl better tolerated particularly with regard to reduced constipation and somnolence	▪	2++
16	Newshan G et al. Transdermal fentanyl for chronic pain in AIDS: a pilot study. J Pain Symptom Manage 2001; 21(1): 69-77	Prospective open-label trial	35 adult patients with AIDS and chronic pain to compare the efficacy of oral morphine with transdermal fentanyl	▪ Pain severity scores decreased significantly with transdermal fentanyl ▪ Mean pain relief scores increased with transdermal fentanyl ▪ Daily functioning measures improved significantly with transdermal fentanyl	▪ Transdermal fentanyl effective for chronic pain in patients with AIDS	2-

HYDROMORPHONE IN THE MANAGEMENT OF MODERATE TO SEVERE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
17	Quigley C. Hydromorphone for acute and chronic pain. Cochrane Database of Systematic Reviews 2006	Systematic review	Systematic review of 48 randomised controlled studies (3510 participants) of the use of hydromorphone in management of acute or chronic pain conditions	▪ Approximately half the studies had a low quality score ▪ In addition, heterogeneity of the studies precluded a meta-analysis ▪ Of the 48 studies, 12 (998 participants) involved chronic pain ▪ 5 trials were placebo controlled; of the remainder hydromorphone was compared with other opioids, bupivacaine and with itself using different formulations ▪ Routes of administration of hydromorphone included IV, oral, spinal, IM and SC	▪ Hydromorphone shown to be a potent analgesic ▪ In terms of analgesic efficacy and tolerability, hydromorphone behaves like other strong opioids ▪ Limited evidence available does not demonstrate any clinically significant difference between hydromorphone and morphine	1++

OXYCODONE IN THE MANAGEMENT OF MODERATE TO SEVERE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
18	Reid CM et al. Oxycodone for cancer-related pain: meta-analysis of randomised controlled trials. Arch Intern Med, 2006; 166(8): 837-843	Systematic review	Systematic review of randomised controlled trials	▪ 4 studies identified comparing oral oxycodone with either oral morphine (n=3) or oral hydromorphone (n=1) suitable for meta-analysis ▪ Overall no evidence that mean pain scores differed between oxycodone and control drugs ▪ In meta-regression analyses, pain scores were higher for oxycodone compared with morphine and lower compared with hydromorphone although	▪ Efficacy and tolerability of oxycodone similar to morphine	1++

METHADONE IN THE MANAGEMENT OF MODERATE TO SEVERE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
19	Nicholson AB. Methadone for cancer pain (review). Cochrane Database of Systematic Reviews 2007	Systematic review	Randomised controlled trials of methadone against active or placebo comparator in adult patients with cancer pain	▪ 9 RCTs with 459 recruits and 392 completing patients ▪ All studies involved active opioid comparators with different dose and titration schedules and various pain scoring scales ▪ Methadone has a similar efficacy to morphine in treating cancer pain ▪ Methadone is no more effective than morphine for cancer-related nerve related pain ▪ Methadone has a similar side-effect profile to morphine but these side-effects may become more prominent with repeated dosing		1++
20	Moryl M et al. Methadone in the treatment of pain and terminal delirium in advanced cancer patients. Palliat Support Care, 2005; 3(4): 311-317	Prospective study	20 adult patients with severe pain and delirium at the end of life who's delirium did not improve 24 hours or longer after starting a neuroleptic drug. Patients rotated or switched to methadone	▪ At 2 weeks 10 patients were no longer alive ▪ Of the 10 patients assessed, 7 were stable on an average of 1.1mg/hour methadone ▪ Of the 20 patients switched to methadone for terminal delirium, pain control was significant in 15, moderate in 3 and unchanged in 2 ▪ Sedation had decreased ▪ Of the 20 patients, improvement of cognitive status was significant in 9, moderate in 6,partial in 2 and none in 3	▪ Most patients had a short-term improvement in mental status as well as significant and lasting improvement in analgesia	3
21	Centeno C et al. Intermittent SC methadone administration in the management of cancer pain. J Pain Palliat Care Pharmacother, 2005; 19(2): 7-12	Open study	10 adult patients with cancer pain well-controlled on oral methadone. Study to look at effectiveness and tolerance of SC methadone as an alternative route in case oral route not available	▪ 2 patients were withdrawn from the study because of non-painful irritation at injection site ▪ 8 patients tolerated repeated administration SC methadone over 7 days ▪ Any local irritation that occurred was managed by changing the injection site and limiting dose to 30mg ▪ In 7/182 repeat administration, injection site changes were necessitated by local irritation ▪ Dose adjustments when changing from oral to SC methadone were minimal		3
22	Fisher K et al. Characterisation of the early pharmacodynamic profile of oral methadone for cancer-related breakthrough pain: a pilot study. J Pain Symptom Manage, 2004; 28(6): 619-625	Open-label non randomised crossover study	37 episodes of breakthrough pain	▪ Onset of analgesic effect of a titrated dose of oral methadone was rapid for all patients ▪ 3/6 study patients experienced an onset of relief by 10 minutes of administration ▪ Adverse effect profile of oral methadone was not different from the patients' usual rescue opioid	▪ Observations suggest that oral methadone can have a rapid onset of analgesic action and may have a role in the management of cancer-related breakthrough pain	3

METHADONE IN THE MANAGEMENT OF MODERATE TO SEVERE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
23	Shir Y et al. Oral methadone for the treatment of severe pain in hospitalised children: a report of 5 cases. Clin J Pain, 1998; 14(4): 350-353	Case series	5 paediatric patients with pain from various causes that is not controlled by non-opioid medications	▪ Treatment with oral methadone (dose range 0.2-0.6mg/kg/day) for time periods of up to 6 weeks resulted in a rapid onset and stable pain relief ▪ No major adverse effects ▪ In 3 of the children, a parent-controlled analgesia regimen was successfully used		3
24	Morley JS et al. Low dose methadone has an analgesic effect in neuropathic pain: a double-blind randomised controlled cross-over trial. Palliat Med, 2003; 17(7): 1-9	Double-blind randomised controlled trial	18 adult patients with a history of more than 3 months of non-malignant neuropathic pain not relieved by other interventions or drug therapies. Randomised to receive placebo or oral methadone. During phase 1 patients received 5mg BD oral methadone, placebo or it was a rest day. During phase 2, the dose of oral methadone was increased to 10mg BD.	▪ Dosing with oral methadone could occur on any of five non-consecutive days during a 20 day period. Rest day after each day of methadone or placebo ▪ Compared with placebo, 10mg BD oral methadone resulted in statistically significant improvements in ratings of maximum pain intensity, average pain intensity and pain relief ▪ Analgesic effects extended over 48 hours as shown by statistically significant improvements in all 3 outcomes on the rest days instituted between each daily dose ▪ Analgesic effects of lowered maximum pain intensity and increased pain relief were also seen with oral methadone 5mg BD but these failed to reach statistical significance ▪ Analgesic effects were not restricted to any particular type of neuropathic pain ▪ One patient withdrew during the 10mg and 6 during the 20mg methadone treatment periods (severe nausea most common reason for withdrawal)	▪ A rest day was instituted between dosing of either placebo or methadone given the long and variable biological half-life of methadone (10-75 hours) ▪ Not using an 'active' placebo may have risked an unintentional 'unblinding' due to side effects	1-

DIAMORPHINE IN THE MANAGEMENT OF MODERATE TO SEVERE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
25	Dickman A et al. The Syringe Driver – Continuous SC infusions in palliative care. 2nd Edition	Expert opinion				4
26	Regnard CF and Hockley J. A guide to symptom relief in palliative care. 3rd Edition	Expert opinion				4
27	Twycross R and Wilcock A. Symptom management in advanced cancer. 3rd Edition	Expert opinion				4

AMITRIPTYLINE IN NEUROPATHIC PAIN: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
28	Saarto and Wiffen. Antidepressants for neuropathic pain (Review). The Cochrane Database of Systematic Reviews 2007	Systematic review	61 randomised controlled trials of 3293 participants reporting the analgesic effectiveness and safety of 20 antidepressant drugs in adult neuropathic pain	▪ Tricyclic antidepressants were found to be effective and have a NNT of 3.6 for at least moderate pain relief ▪ Limited evidence for effectiveness of the newer SSRIs but no studies of SNRIs found	▪ Amitriptyline has the best documented efficacy of the TCAs ▪ Not specific to palliative care	1++
29	Keskinboro K et al. Comparison of gabapentin and amitriptyline in the management of peripheral neuropathic pain. Agri, 2006; 18(2): 34-40	Single centre Double-blind randomised trial	46 adult patients with neuropathic pain randomised to monotherapy with amitriptyline or gabapentin	▪ Both gabapentin and amitriptyline provided effective pain control measured on a visual analog scale ▪ Gabapentin was more effective than amitriptyline in those patients with paroxysmal shooting pain		1-
30	Twycross and Wilcock. Symptom Management in Advanced Cancer. 3rd Edition	Expert opinion				4
31	Regnard and Hockley. A Guide to Symptom Relief in Palliative Care. 5th Edition	Expert opinion				4
32	BNFc 2007	Expert opinion				4

ANTICONVULSANTS IN NEUROPATHIC PAIN: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
33	Wiffen P et al. Anticonvulsant drugs for acute and chronic pain (Review). The Cochrane Database of Systematic Reviews 2005	Systematic review	23 randomised trials (1074 adult participants) of 6 anticonvulsants	▪ Although anticonvulsants are widely used in chronic pain, few trials actually show analgesic effectiveness ▪ No evidence that anticonvulsants are effective in acute pain	▪ Based on this evidence, the authors advise that in chronic pain syndromes other than trigeminal neuralgia, anticonvulsants should be withheld until other interventions have been tried ▪ While gabapentin is increasingly used, the evidence would suggest it is not superior to carbamazepine ▪ The efficacy of gabapentin and carbamazepine have been individually assessed in the Cochrane reviews listed below	1++

CARBAMAZEPINE IN NEUROPATHIC PAIN: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comments**	**Grade of Evidence**
34	Wiffen PJ et al. Carbamazepine for acute and chronic pain (Review). Cochrane Database of Systematic Reviews 2005	Systematic review	12 randomised controlled trials of adult patients with neuropathic pain. Migraine and headache studies were excluded	12 studies with 404 participants identified Approximately two-thirds of patients who take carbamazepine for neuropathic pain can expected to achieve good pain relief Carbamazepine is not effective in acute pain	Number of participants was small ranging from 9 to 71 Poor quality reporting limited the ability to combine data Usual clinical decision is a choice between an antidepressant and an anticonvulsant as first-line treatment	1++
35	BNFc 2007	Expert opinion				4
36	Regnard and Hockley. A guide to symptom relief in palliative care. 5th Edition	Expert opinion				4

GABAPENTIN IN NEUROPATHIC PAIN: SUMMARY OF EVIDENCE						
	Reference	**Study type**	**Subjects**	**Results**	**Comments**	**Grade of Evidence**
37	Wiffen PJ et al. Gabapentin for acute and chronic pain (Review). Cochrane Database of Systematic Reviews 2005	Systematic review	15 randomised controlled trials trials of 1468 adult patients to assess the effectiveness and adverse effects of gabapentin for pain management in clinical practice	▪ In those studies reporting on chronic pain, NNT in all trials with evaluable data is 4.3 ▪ 42% patients improved on gabapentin compared with 19% of those on placebo ▪ NNH for adverse effects leading to withdrawal from a trial was not significant	▪ One study was of acute pain, one chronic cancer pain and the remainder chronic pain in a variety of conditions ▪ Gabapentin shown to be effective in management of chronic pain ▪ Gabapentin is not effective in the management of acute pain ▪ In studies included, gabapentin was assessed as monotherapy not as adjunctive therapy with for example opioids	1++
38	Gilron I et al. Morphine, gabapentin or their combination for neuropathic pain. NEJM, 2005; 325(13): 1324-35	Randomised, double-blind, active, placebo-controlled, four-period crossover trial	57 adult patients with painful diabetic neuropathy or postherpetic neuralgia given placebo (lorazepam), S/R morphine, gabapentin and a combination of gabapentin and morphine, each given orally for 5 weeks	▪ 41 patients completed the trial ▪ Gabapentin and morphine combined achieved better analgesia at lower doses of each drug than either as a single agent ▪ Gabapentin-morphine combination resulted in a higher frequency of constipation than gabapentin alone and a higher frequency of dry mouth than morphine alone		1+
39	Keskinbora K et al. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomised open trial	Randomised open trial	75 adult cancer patients with neuropathic pain despite opioid therapy randomised to continued monotherapy with an opioid or adjunctive therapy of gabapentin with the opioid	▪ 63 patients completed the study ▪ Combination of morphine and gabapentin provided better relief of neuropathic pain in cancer patients than opioid monotherapy ▪ Rate of side-effects significantly lower in the combination group than in the opioid monotherapy group		2+
40	Keskinboro K et al. Comparison of gabapentin and amitriptyline in the management of peripheral neuropathic pain. Agri, 2006; 18(2): 34-40	Single centre Double-blind randomised trial	46 adult patients with neuropathic pain randomised to monotherapy with amitriptyline or gabapentin	▪ Both gabapentin and amitriptyline provided effective pain control measured on a visual analog scale ▪ Gabapentin was more effective than amitriptyline in those patients with paroxysmal shooting pain		1-
41	Butkovic D et al. Experience with gabapentin for neuropathic pain in adolescents: report of 5 cases. Paediatr Anaesth, 2006; 16(3): 325-329	Case series	5 adolescent patients with intractable neuropathic pain. 4 patients were cancer patients and one suffered from neuropathic pain in the neck	▪ Visual analog scores of pain completed before and during treatment showed a rapid improvement in all patients ▪ Minimal side-effects		3

GABAPENTIN IN NEUROPATHIC PAIN: SUMMARY OF EVIDENCE						
	Reference	**Study type**	**Subjects**	**Results**	**Comments**	**Grade of Evidence**
42	BNFc 2007	Expert opinion				4

DEXAMETHASONE AS AN ADJUNCT ANALGESIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
43	Hardy JR et al. A prospective survey of the use of dexamethasone on a palliative care unit. Palliative Med 2001; 15: 3-8	Prospective study	106 adult patients with advanced malignant disease started on glucocorticoids were surveyed each week to document the indications for use, any benefical effect, any toxicity incurred and the reason for stopping	▪ Most patients had several indications for starting dexamethasone ▪ Specific indications – spinal cord compression, cerebral metastases, lymphangitis carcinomatosa, intestinal obstruction, obstructive lymphadenopathy, liver metastases, obstruction of superior vena cava ▪ Non-specific indications anorexia (n=47 19%), nausea (n=31 12%), mood/well-being (n=31 12%), neuropathic pain (n=19 7%), vomiting (n=18 7%), bone pain (n=16 6%), dyspnoea (n=15 6%), weakness (n=10 4%), liver pain (n=9 4%), pain not otherwise specified (n=4 2%), other (n=2 1%) ▪ Median duration of steroid use was 21.5 days (range 1-89 days) ▪ Most common reason for stopping was death or deterioration of condition (48%). 16 % weaned off after a planned course and only 4 patients discontinued because of unacceptable side effects ▪ Majority of patients complaining of anorexia, nausea, pain, low mood, vomiting and weakness appeared to have a beneficial response at some stage whilst taking steroids ▪ Patients complaining of shortness of breath or poor mobility had o change or a worsening of their symptom scores with steroid therapy ▪ Use of prophylactic nystatin to prevent candidiasis was encouraged	▪ Authors comment that there is little evidence base to support this frequent use in many of the non-specific indications listed ▪ Survey suggests many non-specific symptoms did improve with steroid treatment but this does not constitute reliable evidence. This study was uncontrolled and assessment of symptom response does not take into account other treatments the patient may have been receiving ▪ Overall conclusion from authors is that the benefit of therapy with steroids in patients with advanced cancer probably outweighs any side-effects. The lowest effective dose should be used and therapy discontinued if no benefit obtained or any initial benefit is lost. Patients should be followed closely on a regular basis.	3

DEXAMETHASONE AS AN ADJUNCT ANALGESIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
44	Gannon C et al. A retrospective observation of corticosteroid use at the end of life in a hospice. J Pain and Symptom Manage 2002; 24(3): 328-334	Retrospective review of deaths occurring over a 6 month period to clarify present use of corticosteroid therapy	Notes of 178 adult patients reviewed	▪ 90 patients (50.6%) received corticosteroids during their terminal admission ▪ Of these, treatments included dexamethasone (n=77), prednisolone (n=13) and parenteral corticosteroids (n=3) ▪ Documentation of the indication for steroid use was clear in the notes for 67%, deduced for 9% and not clear for 24% ▪ Observed indications raised ICP (24%), boost/improve well-being (22%), pain (mainly liver pain 13%), disease modification (13%), post-radiotherapy (10%), dyspnoea (7%), anorexia (4%), superior vena cava obstruction (3%), spinal cord compression (3%) ▪ Main reason for withdrawal of steroids was loss of oral route (79% cases). Failed therapeutic response in 7% with no evident reason for stopping in remaining 14%	▪ High prevalence of corticosteroid use in the terminal phase, even until death contrasting with near absolute withdrawal of corticosteroids once the oral route was lost ▪ Authors suggest that in a number of patients, particularly those receiving longer-term corticosteroids for non-specific indications, these drugs could have been safely discontinued before the terminal phase as any short-term benefits would have waned. This would have prevented unnecessary toxicity and avoided difficult management decisions surrounding steroids around time of death ▪ In those patients who require continued steroid use to control symptoms therapy should be switched to the parenteral when the oral route becomes unavailable	3
45	Twycross R. The risks and benefits of corticosteroids in advanced cancer. Drug Safety 1994; 11(3): 164-178	Review article		▪ Use of corticosteroids in advanced cancer can be grouped into 4 categories – specific; pain relief; hormone therapy; general (improved appetite, enhance sense of well-being, improve strength) ▪ Corticosteroids have many potential side-effects and complications		4
46	Mercadante S et al. The use of corticosteroids in home palliative care. Support Care Cancer 2001; 9: 386-389	Open label longitudinal study of 376 consecutive patients	Considered 152 patients requiring steroid treatment; 102 who were already receiving steroids before entering the initial study were excluded. Evaluation of 50 adult palliative patients who received corticosteroid therapy	▪ Statistically significant improvements in the intensity of anorexia, weakness, headache and nausea and vomiting associated with cerebral involvement or bowel obstruction ▪ Intensity of dyspnoea also improved after corticosteroid therapy ▪ In most cases a favourable outcome was considered to have been reached within 2-3 days (range 1-5 days) ▪ Dexamethasone was the most frequently used steroid ▪ Steroids never prescribed to improve pain relief. However, their administration was found to be correlated with a decrease in pain intensity ▪ Steroid treatment was maintained up to the time of death in ~ 50% patients. Stopped in 10 patients as ineffective		2-

DEXAMETHASONE AS AN ADJUNCT ANALGESIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
47	Needham PR et al. Steroids in advanced cancer: survey of current practice. BMJ, 1992; 305:999	Case review	100 adult patients consecutively admitted to a hospice	▪ 33 patients were taking steroids at time of admission ▪ Most had been taking for more than 1 month ▪ Most common reasons for use – anorexia/weakness and raised ICP ▪ 10 patients admitted from hospice home-care team with detailed notes ▪ Of the other 23 patients, only 2 had accompanying documentation giving indications for and dose of steroids ▪ In most cases, the response to steroids did not seem to have been monitored ▪ Of the 28 patients who could answer questions only 8 felt steroids had been beneficial, 9 were uncertain, 11 did not perceive any benefit	▪ Steroids can be prescribed for a number of reasons in advanced malignancy – best known being their stimulant effect in anorexia and weakness and to reduce oedema around cerebral tumours ▪ Suggested to confer benefit in ~ 40% patients overall but particularly when used for more than 1 month can have severe adverse effects as well as adding to drug load ▪ Patients should be closely monitored ▪ No universally accepted dose but suggest 4mg dexamethasone daily in anorexia and 16mg dexamethasone daily for reduction of cerebral oedema or for spinal cord compression ▪ Results should be assessed after 1 week when the drug should be stopped if there has been no therapeutic response ▪ If there is a clinical response, reduce dose to minimum dose which maintains benefit ▪ Patient and/or family should be made aware of dangers of stopping steroids suddenly ▪ Response and adverse effects should be closely recorded	3

DEXAMETHASONE AS AN ADJUNCT ANALGESIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
48	Twycross R. Corticosteroids in advanced cancer. BMJ, 1992; 305: 969-970	Review article		▪ General effects of corticosteroids include improved appetite, mood and strength ▪ Effects of steroids diminish with time ▪ Reason for prescribing should be clearly stated ▪ Except where the aim is to control the tumour, the corticosteroid should be prescribed initially on a trial basis for no more than a week; the chances of obtaining a better response after this time are poor. Treatment should only be continued if subjective or objective benefit occurs. ▪ Using corticosteroids for their general effects should be avoided as far as possible in anxious patients and in patients with diabetes because of the risk of worsening the associated condition ▪ No evidence that IV regimen is superior to the use of oral dexamethasone or prednisolone in terms of pain relief or general benefit and is not recommended as routine ▪ Corticosteroids have been shown to reduce pain in various situations. Major mode of action likely to be anti-inflammatory but there is also a possible central analgesic effect. Corticosteroids may be administered as a co-analgesic in situations where there is a large tumour mass within a relatively confined space when, as a result of inflammation, there is pressure on neighbouring veins and lymphatics (e.g. raised ICP as a result of a brain tumour). Also of potential use in relieving nerve compression pains that do not respond to opioids alone ▪ Use in symptomatic brain tumours – corticosteroids reduce reactive oedema around the tumour, reduce cerebral blood flow and sometimes have a cytostatic or cytotoxic effect. Maximum beneficial dosage not fully known; also need to consider increased likelihood of unacceptable side effects with increasing doses ▪ Corticosteroids shown to be effective in treating hypercalcaemia associated with myeloma and lymphoma – not shown to be particularly effective for hypercalcaemia associated with most solids tumours (bisphosphonates are more increasingly used) ▪ Corticosteroids shown to be effective adjuncts as anti-emetics although no generally accepted hypothesis to explain mode of action ▪ Choice of corticosteroid arbitrary and choice between dexamethasone and prednisolone likely to be determined by fashion, cost and availability ▪ Dexamethasone tablets dissolve readily in water and a large number can be given in a small volume of water ▪ Choice of starting dose arbitrary ▪ Given the long duration of action of corticosteroids (other than hydrocortisone), unless the number of tablets preclude single administration, the dose can be given as a single dose at breakfast ▪ Except where tumour control is the objective, corticosteroid should be prescribed initially on a trial basis for 1 week because the chances of obtaining a better response after this time are poor		4

DEXAMETHASONE AS AN ADJUNCT ANALGESIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
49	Bruera E et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. Cancer Treat Rev 1985; 69: 751-754	Randomised, double-blind crossover trial	40 terminally ill adult cancer patients comparing oral methylprednisolone against placebo for the relief of pain and other symptoms (psychiatric status, appetite, nutritional status, daily activity and performance). On day 0 patients randomized to oral methylpred or placebo; days 5-7 were treatment free and cross-over was made for days 8-12. On day 13, the double-blind phase of the study was completed and all patients were given methylpred for 20 days	▪ 9 patients did not complete the trial ▪ Intensity of pain significantly lower after methylpred as compared with baseline or placebo ▪ Other parameters that showed significant improvement were depression, appetite and food consumption ▪ Anxiety and performance status did not show significant improvements with methylpred compared to baseline or placebo ▪ All parameters sensitive to methylpred reached maximum improvement during the first phase of the study ▪ Of the 8 patients who had not experienced any benefit during initial phase of trial, none showed any improvement in open phase ▪ Effect on most parameters had deteriorated slightly by day 33 compared to day 5 (in spite of significant improvement at day 33 compared to baseline) ▪ Methylpred not associated with marked toxicity	▪ Pain was the end point most sensitive to methylpred treatment followed by depression, appetite and food consumption ▪ Anxiety and performance status were insensitive to methylpred treatment ▪ Methylpred exerts its action rapidly and chances of obtaining better responses after 5 days of treatment are poor ▪ 8/23 patients who initially responded significantly to methylpred showed disappearance of the symptomatic benefits by day 33 – not sure whether this is due to loss of effect of methylpred with time or to the natural disease progression	1-
50	Shih A et al. Role of corticosteroids in palliative care. J Pain and Palliative Care Pharmacotherapy, 2007; 21(4): 69-76	Review article		▪ Corticosteroids can be used for a number of symptoms ▪ Corticosteroids are one of the most frequently prescribed medications in the palliative care setting ▪ Although not significantly better than other existing therapies for single symptom control, corticosteroids can be used when patients have multiple symptom control		4
51	Farr WC. The use of corticosteroids for symptom management in terminally ill patients. Am J Hosp Care, 1990; 7(1): 41-46	Retrospective chart review	425 adult patients admitted to this hospice	▪ 22/425 (5%) patients taking a corticosteroid at time of admission and majority of these had intracranial disease ▪ 121 (285) entering the inpatient unit considered candidates for steroids ▪ Of those patients given oral prednisolone as an appetite stimulant, 66% responded with virtually all of the patients who responded doing so within a few days of beginning treatment. The earlier treatment was started, the more likely the patients were to respond ▪ Of 9 patients given parenteral steroids for partial bowel obstruction, 6 had symptomatic improvement of symptoms ▪ Of the 121 patients, 11 experienced side effects that could be attributed to the treatment		3

DEXAMETHASONE AS AN ADJUNCT ANALGESIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
52	Hanks GW et al. Corticosteroids in terminal cancer: a prospective analysis of current practice. Postgrad Med J 1983; 59: 702-706	Prospective analysis	373 adult patients over a period of 16 months	▪ 218 patients (58%) received corticosteroids ▪ Usual starting dose prednisolone was 10-30mg daily (n=121) and of dexamethasone 4-16mg daily (n=68) ▪ Higher doses of dexamethasone were used mainly for raised ICP or spinal cord compression ▪ Maintenance dose varied considerably between patients ▪ Main indications – non specific tonic, nerve compression, raised ICP, airway obstruction, metastatic arthralgia ▪ Tonic – 22/58 who received prednisolone and 7/17 who received dexamethasone were considered to respond ▪ Nerve compression – 8/21 who received prednisolone and 8/13 who received dexamethasone considered to respond ▪ Raised ICP – 10/23 who received dexamethasone considered to respond ▪ Side effects common with both drugs – no significant difference between them ▪ Duration of treatment ranged from 1 day to almost 11 years; median duration was between 4 and 8 weeks	▪ Overall, corticosteroids produced a good response in 4/10 patients. For certain conditions such as nerve compression pain, there is a substantially higher response rate ▪ At time of this study, the usual choice of corticosteroid in this hospice was soluble prednisolone except in certain circumstances when dexamethasone was used instead – raised ICP, spinal cord compression or uncomplicated nerve compression ▪ Choice of soluble prednisolone based on familiarity and cost but in actual fact soluble form of prednisolone is much more expensive than dexamethasone in equivalent doses ▪ From results of study, dexamethasone appears to have several advantages over prednisolone. It is as effective as prednisolone for all indications compared and may be more effective in the relief of pressure symptoms related to a tumour mass. Incidence of side-effects similar. Dexamethasone is cheaper than soluble prednisolone (although not standard prednisolone). Fewer tablets need to be taken by the patient because of its greater potency.	2-
53	Mercadente SL, Berchovich M, Casuccio A et al. A prospective randomised study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients. Am J Hosp Palliat Care 2007; 24(1): 13-9	Randomised controlled trial	76 adult advanced cancer patients with pain	▪ Patients randomized to receive conventional opioid treatment or conventional opioid treatment pluse dexamethaone 8mg orally ▪ No differences in pain intensity, opioid consumption, opioid escalation index in 66 evaluable patients ▪ Corticosteroids appeared to persistently decreased opioid related gastrointestinal symptoms and improved sense of wellbeing	▪ Authors conclude that any analgesic benefits of corticosteroids may be limited to patients with neuropathic pain ▪ Sample size may have been too small to detect any significant benefits of corticosteroids	

NON STEROIDAL ANTI-INFLAMMATORY DRUGS AS AN ADJUNCT ANALGESIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
54	McNichol E, Strassels SA, Goudas L et al. NSAIDS or paracetamol alone or in combination with opioids for cancer pain. Cochrane Database of Systematic Reviews 2005	Systematic review	42 trials involving 3084 patients with cancer pain receiving NSAIDS or paracetamol alone or in combination with opioids	▪ Clinical heterogeneity of study methods and outcomes precluded meta-analysis ▪ 7 out of 8 papers that compared NSAID with placebo demonstrated superior efficacy of NSIAD with no difference in adverse effects ▪ There was no clear evidence to suggest superiority of one NSAID over another ▪ 9/14 papers suggested a slight but statistically significant advantage of between NSAID in combination with an opioid versus either single entity	▪ Heterogeneity and short duration of studies limits generalization of their findings	1++

Anorexia and weight loss

NO PHARMACOLOGICAL AGENT RECOMMENDED

DEFINITION

Cancer cachexia is a complex syndrome characterised by progressive tissue nutritional depletion and decreased nutrient intake manifest as anorexia (loss of appetite) and profound weight loss.

SCOPE

- Reduced food and fluid intake is normal at the end of life.
- Treatment of anorexia and weight loss may not be appropriate if these symptoms are not having a direct impact on quality of life
- Management of anorexia and weight loss include identification and, if appropriate, treatment of possible underlying cause(s)
- Pharmacological management of anorexia and weight loss may be appropriate if treatment of the underlying cause is not possible or is not effective
- Here we consider only pharmacological management of anorexia and weight loss

OVERVIEW OF MANAGEMENT OPTIONS

CLASSES OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

- Megestrol acetate (but see below – no evidence to support use in the paediatric population)
- Corticosteroids (dexamethasone)

MEGESTROL ACETATE IN THE MANAGEMENT OF ANOREXIA AND WEIGHT LOSS IN PALLIATIVE CARE

Recommendations
Meta-analysis shows a benefit of megestrol acetate in adult patients with a clinical diagnosis of anorexia-cachexia related to cancer [55]
The small number of patients and poor quality of studies has not enabled any recommendations of megestrol acetate in adult patients with anorexia related to AIDS or any other underlying pathology [55]
Insufficient evidence to define the optimal dose of megestrol acetate in adults [55] [56]

Evidence for management of this symptom with this drug in children
Evidence to support the use of megestrol acetate in children is limited to case series. However in children with cancer reports of profound adrenal suppression with megestrol acetate suggest that this drug needs to be used with caution [59].

Where this alone is insufficient: evidence for management of this symptom in adults
In adults the anabolic steroid megestrol acetate has been demonstrated to have beneficial effects on appetite and weight gain but the effects on quality of life are less well established [55].

CORTICOSTEROIDS IN THE MANAGEMENT OF ANOREXIA AND WEIGHT LOSS IN PALLIATIVE CARE

Recommendations
Systematic review of small number of adult studies suggest oral or parenteral corticosteroids may be of use in the short term management of anorexia in palliative care [60]
Optimal dose and duration of therapy with corticosteroids has not been established [60]
No studies in children identified

Evidence for management of this symptom with this drug in children
No studies of corticosteroids for this indication in children identified.

Where this alone is insufficient: evidence for management of this symptom in adults
- Although used in some adult patients with anorexia, there is little evidence base to support the use of corticosteroids in this indication.
- Anorexia may be linked with low cortisol levels which may be improved with corticosteroid therapy.
- The optimal dose and duration of therapy in adults is not known but only short courses (~2 weeks) are suggested as the benefits diminish after ~ 4 weeks.

Additional supporting information for this drug

DEXAMETHASONE
Corticosteroids have a number of potential roles in palliative care although good quality supporting evidence is weak
- Specific e.g. nerve compression, dyspnoea, raised ICP
- Pain relief
- Anticancer hormone therapy
- General e.g. anorexia and to enhance sense of wellbeing

Dexamethasone is likely to be included in the EMLc for palliative care and, under specialist guidance, may be used for a number of symptoms.

MEGESTROL ACETATE IN ANOREXIA WEIGHT LOSS IN PALLIATIVE CARE; SUMMARY OF THE EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
55	Berenstein EG et al. Megestrol acetate for treatment of anorexia-cachexia syndrome (Review). Cochrane Database of Systematic Reviews 2005 (update 2006)	Systematic review	32 double-blind, single-blind or unblinded studies that assessed megestrol acetate with placebo or other drug treatments. 22 trials compared megestrol acetate at different doses with placebo, 5 compared different doses of megestrol acetate versus other drugs, 2 compared megestrol acetate with other drugs and placebo and 5 compared different doses of megestrol	▪ Megestrol acetate improves appetite and weight gain in patients with anorexia-cachexia syndrome related to cancer ▪ Not enough evidence to reach a conclusion about the effect on quality of life or the optimal dose ▪ Too little information on AIDS patients or those patients with other underlying pathologies	▪ Adult patients ▪ 4826 patients in total ▪ 685 included studies assessed as moderate or low quality trials	1++
56	Santucci G et al. Common gastrointestinal symptoms in pediatric palliative care: nausea, vomiting constipation, anorexia, cachexia. Pediatr Clin North Am, 2007; 54: 673-689	General review article		▪ Megestrol acetate 7.5-10mg/kg/day in 1-4 divided doses; maximum 800mg/day or 15mg/kg/day ▪ Titrate dose to response, weight gain seen in 2-4 weeks; limited data in children		4
57	Regnard and Hockley. A guide to symptom relief in palliative care. 5th Edition	Expert opinion			Anorexia may be linked to low cortisol levels and dexamethasone or prednisolone can improve anorexia. Progestins are effective and megestrol acetate 800mg daily has the same effect on anorexia as 3mg dexamethasone daily but is much more expensive	4
58	Twycross and Wilcock. Symptom management in advanced cancer 3rd Edition	Expert opinion			Appetite stimulants are appropriate in only a minority of anorexic patients. If used, they should be closely monitored and stopped if no benefit is perceived after 1-2 weeks. Progestogen e.g. megestrol – the effect may last for months and generally is associated with weight gain (Corticosteroids – useful in about 50% of patients but the effect generally lasts for only a few weeks)	4
59	Orme LM, Bond JD, Humphreys MS et al. Megestrol acetate in pediatric oncology patients may lead to severe symptomatic adrenal suppression. Cancer 2003; 98(2): 397-405	Case series	19 paediatric oncology patients treated with megestrol acetate	▪ Treatment with megestrol acetate was associated with significant increases in weight, appetite and caloric intake ▪ 10 of 11 patients tested demonstrated a significant and potentially dangerous decrease in cortisol ▪ 1 patient manifested clinical hypoadrenalism with haemodynamic collapse requiring inotropic support		

CORTICOSTEROIDS IN ANOREXIA AND WEIGHT LOSS IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
60	Yavuzsen T et al. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol, 2005; 23(33): 8500-11	Systematic review	Six studies of adult patients of 647 patients comparing methylprednisolone, prednislone or dexamethasone with placebo	▪ 3 studies comparing IV or oral methylprednisolone with placebo in 402 adult patients. Two multicentre studies used IV methylprednisolone and measured QOL in preterminal cancer. Both found IV methylprednisolone improved appetite, pain, QOL, vomiting and well-being. Weight was not statistically changed. In a 14 day randomised double-blind cross-over trial that compared oral methylprednisolone 16mg/dose BD with placebo, appetite and performance status improved ▪ Single study comparing oral prednisolone with placebo in 61 adult patients. Dose of 10mg/day for 6 weeks. Results showed a significant improvement in appetite and well-being in those taking prednisolone. However, most patients enrolled were also receiving chemotherapy. Two studies compared dexamethasone with placebo. In total 184 patients were included with doses ranging from 3-8mg/day and study duration ranging from 4 days to death. One study was IV and the other oral. One study found a significant improvement after 2 weeks but this disappeared by 4 weeks. In the other study, dexamethasone was beneficial in reducing post chemotherapy side-effects including anorexia.	▪ Dosage and type of corticosteroid differed between studies such that the optimal dose and duration of therapy are unknown. Short courses (e.g. 2 weeks) are recommended because benefits diminish after 4 weeks	1+
61	Santucci G et al. Common gastrointestinal symptoms in pediatric palliative care: nausea, vomiting constipation, anorexia, cachexia. Pediatr Clin North Am, 2007; 54: 673-689	General review article		▪ Corticosteroids improve appetite and well-being. No lasting improvement in nutritional status. Decrease proinflammatory cytokine. Inhibit prostaprime metabolism. ▪ Dose of dexamethasone <10kg 0.15mg/kg/dose BD; 10-20kg 2mg/dose BD; 21-40kg 4mg/dose BD; >41kg 8mg/dose BD ▪ Dose of prednisolone 0.05-2mg/kg/DAY in 1-4 divided doses		4
62	Moertel C et al. Corticosteroid therapy of preterminal gastrointestinal cancer. Cancer 1974; 33: 1607-1609		116 adult patients with advanced GI cancer. Compared dexamethasone 0.75mg/dose QDS and dexamethasone 1.5mg/dose QDS	▪ After 2 weeks there was a significant improvement in appetite and strength in patients receiving dexamethasone – this improvement disappeared after 4 weeks of treatment		2-

Delirium and terminal agitation

Recommendations for Inclusion: HALOPERIDOL AND MIDAZOLAM

New medicines for addition to EMLc: Midazolam

New formulations for addition to EMLc:
Midazolam injection 1mg/ml and 5mg/ml

DEFINITION

- Delirium (acute confusion) is common in the terminal stages of advanced disease and is associated with a short prognosis. Features suggested to be highly specific to acute delirium states are acute onset, fluctuating course, disorganised thinking, inattention, memory impairment and disorientation.
- Delirium at end of life may be associated with agitation (terminal agitation) or lethargy

SCOPE

- Management of delirium comprises identification and wherever possible treatment of possible underlying cause(s)
    - Medicines
    - Organ failure
    - Hypoxia
    - Infection
    - Hypercalcaemia
    - Electrolyte disturbance
- Delirium is commonly caused by medicines and the child's current medicines should be reviewed before pharmacological management is initiated
- Where treatment of the underlying cause(s) of delirium is not possible or unsuccessful pharmacological management is necessary

OVERVIEW OF MANAGEMENT OPTIONS

CLASSES OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

- Antipsychotics
- Benzodiazepines

HALOPERIDOL IN THE MANAGEMENT OF DELIRIUM / AGITATION IN PALLIATIVE CARE

Recommendations
Haloperidol is considered as first choice therapy in the management of confusion during the terminal phases of disease [63] [64] [65] [66] [67]
Haloperidol has been shown to be effective in the management of confusion in adult patients during the terminal phases of disease [63]
Efficacy and use in children is based on clinical experience and opinion [67] [68] [69] [70]

Evidence for management of this symptom with this drug in children

- Evidence from a cohort study of 40 children [70] supports the use of haloperidol in management of acute delirium in critically ill children in the intensive care setting.
- Haloperidol is included in the EMLc for use in psychotic disorders in children

Where this alone is insufficient: evidence for management of this symptom in adults
Despite the absence of good quality clinical trials, haloperidol appears to be widely used in the management of delirium and confusion in palliative care

Additional supporting information for this drug

HALOPERIDOL
- Haloperidol is currently included in the EMLc for management of psychotic disorders; preparations: oral liquid 2mg/ml; tablets/capsules 0.5mg, 2mg, 5mg; injection 5mg/ml
- Widely available
- Available in UK, USA and Australia as both oral (enteral) and parenteral formulations
- Licensed in UK from 2 years of age for behavioural disorders; in the USA from 3 years of age and in Australia from 5 years of age
- Cheap
- Potential role in confusion/delirium; anxiety and as an antiemetic
- Oral bioavailability 60-70%
- Onset of action 10-15 minutes if given SC; >1hour if given orally
- Time to peak plasma concentration 10-20 minutes SC and 30-40 minutes if given orally
- Duration of action up to 24 hours, sometimes longer
- Risk of extrapyramidal side-effects
- Compared with chlorpromazine, has less effect on the cardiovascular system
- No antimuscarinic properties

BENZODIAZPINES IN THE MANAGEMENT OF DELIRIUM / AGITATION IN PALLIATIVE CARE

Recommendations
As monotherapy, benzodiazepines may aggravate rather than alleviate delirium [71]
Expert opinion supports the addition of midazolam when haloperidol is insufficient to control agitated delirium [66] [69]
Systematic review evidence suggests benzodiazepines may have a role in management of agitated delirium [70]

Evidence for management of this symptom with this drug in children
Evidence for use in children is extrapolated from adult data and from clinical experience and opinion.

Where this alone is insufficient: evidence for management of this symptom in adults
- Where agitation and terminal restlessness persists despite identification and treatment of possible underlying causes, expert opinion supports the use of benzodiazepines for their anxiolytic sedative properties.
- In combination, benzodiazepines appear to act synergistically with haloperidol and can result in greater clinical effect than haloperidol alone. However, as sole therapy, benzodiazepines may aggravate rather than alleviate delirium.
- No evidence of improved efficacy or safety of one benzodiazepine over another was identified.
- The choice of benzodiazepine for inclusion in the EMLc for palliative care is therefore determined by the availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.

Additional supporting information for this drug

MIDAZOLAM

- Midazolam can be administered subcutaneously and as a continuous infusion with other medication for symptom management when the enteral route is no longer available.
- Midazolam can also be administered via the buccal route with rapid onset and ease of administration.
- There is evidence to support the safety of administration of midazolam via the buccal route in children.

HALOPERIDOL IN THE TREATMENT OF DELIRIUM/ AGITATION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
63	Jackson KC and Lipman AG. Drug therapy for delirium in terminally ill patients (Review). The Cochrane Database of Systematic Reviews 2004	Systematic review	Primary objective was to identify and evaluate studies examining medications used to treat patients suffering from delirium during the terminal phases of disease. Prospective studies with or without randomisation and/or blinding.	▪ Only 1 study met the criteria ▪ Compared chlorpromazine, haloperidol and lorazepam in 30 hospitalised adult AIDS patients ▪ Data from this single study suggests that haloperidol is the most suitable drug therapy; chlorpromazine may be an acceptable alternative ▪ The lorazepam arm of this study was stopped due to excess sedation	▪ Further research needed but authors comment on the considerable ethical problems in undertaking a clinical trial of effective treatment of such a symptom in this group of patients	1++
64	Vela-Brincat J et al. Haloperidol in palliative care. Palliative Med 2004; 18: 195-201	General review article			▪ Supports use of haloperidol	4
65	Centeno C et al. Delirium in advanced cancer patients. Palliative Med 2004; 18: 184-194	General review article			▪ Supports use of haloperidol	4
66	Twycross and Wilcock. Symptom management in advanced cancer. 3rd Edition	Expert opinion			▪ In general, haloperidol is the drug of choice for delirium. It is as effective as phenothiazines such as chlorpromazine but is safer to use. Can be given by oral, rectal, SC, IM and IV routes	4
67	Regnard and Hockley. A guide to symptomatic relief in palliative care. 5th Edition	Expert opinion			▪ Supports use of haloperidol	4
68	BNFc 2007	Expert opinion			▪ Supports use of haloperidol	4
69	Jassal SS. Basic symptom control in paediatric palliative care. The Rainbows Children's Hospice Guidelines 7th Edition 2008	Expert opinion			▪ Supports use of haloperidol	4
70	Scheiveld JN, Leroy PL, van Os J et al. Pediatric delirium in critical illness: phenomenology, clinical correlates and treatment response in 40 cases in the pediatric intensive care unit	Case series	40 consecutive patients in tertiary PICU referred to psychiatric team because of delirum	▪ 27 patients received haloperidol ▪ 10 patients received risperidone ▪ 1 patient received both drugs ▪ 2 children who received haloperidol experienced acute torticolis. ▪ No details on the dose of drugs are given	▪ Supports the use of haloperidol although adverse effects are a concern	

BENZODIAZPINES IN THE TREATMENT OF AGITATED DELIRIUM IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
71	Kehl KA. Treatment of terminal restlessness: a review of the evidence. J Pain Palliat Care Pharmacother 2004; 18(1): 5-30	Systematic review	Purpose of the review was to examine the empiric evidence about the pharmacological treatment for terminal restlessness	▪ Of 72 articles reviewed 14 met the study criteria ▪ Evidence identified to support the use of neuroleptic medication, benzodiazepines and phenothiazines alone or in combination ▪ Evidence was limited to case reports, case series and concurrent observations	▪ Further research needed ▪ Insufficient evidence to recommend a single medication or class of medications appropriate for terminal restlessness	2++

Breathlessness (dyspnoea)

Recommendations for Inclusion: MORPHINE, DIAZEPAM AND MIDAZOLAM

New medicines for addition to EMLc: Midazolam

New formulations for addition to EMLc:
Morphine sulphate modified release granules 20mg, 30mg, 60mg, 100mg and 200mg
Midazolam injection 1mg/ml and 5mg/ml
Diazepam rectal tubes 2.5mg, 5mg and 10mg

DEFINITION

Breathlessness (dyspnoea) is the unpleasant sensation of being unable to breathe adequately. It is a common symptom and increases in prevalence and severity as disease progresses. Anxiety is often a major component of breathlessness.

SCOPE

- Breathlessness is a complex multidimensional symptom with physical psychological and spiritual dimensions
- Pharmacological palliation of breathlessness is only appropriate when any potentially reversible underlying cause of this symptom has been identified and treated
- Pharmacological management should be accompanied by appropriate non pharmacological measures including
    - Anxiety management
    - Adaptation of the environment
- Here we consider only pharmacological management

OVERVIEW OF MANAGEMENT OPTIONS

CLASSES OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN:

- Strong opioids
- Benzodiazepines
- *Oxygen
- *Bronchodilators
- *Corticosteroids

(*These are currently included in the EMLc for management of respiratory symptoms: no further work done on these.)

STRONG OPIOIDS IN THE MANAGEMENT OF BREATHLESSNESS

Recommendations
Oral and parenteral opioids are effective in the treatment of breathlessness in adults [72] [73]
No evidence has been identified that nebulised opioids are more effective than placebo in the management of breathlessness in adults [72][73][74]

MORPHINE IN MANAGEMENT OF BREATHLESSNESS

Recommendations
Oral and parenteral morphine is effective in the treatment of breathlessness in adults [72] [73] [74] [75]
Evidence of effectiveness of morphine in breathlessness in children is limited to case reports [76] [77], expert opinion and data extrapolated from adults
Given the inclusion of oral and parenteral forms of morphine in the EMLc, inclusion of morphine as an option for treatment of breathlessness seems appropriate

Evidence for management of this symptom with this drug in children
The evidence for effectiveness of morphine in children with breathlessness is limited to case reports, expert opinion and data extrapolated from adults.

Where this alone is insufficient: evidence for management of this symptom in adults
- In a systematic review and meta-analysis enteral or subcutaneous strong opioids have been shown to significantly improve the sensation of dyspnoea in adults with advanced disease
- There is no evidence to support the use of nebulised opioids in the management of dyspnoea
- When administered at appropriate doses opioids reduce rate of breathing and sensation of dyspnoea without measurable changes in oxygen saturation or pCO2 [83]
- There is a lack of consistent evidence to support use of opioids by any route to improve exercise tolerance.

Additional supporting information for this drug

MORPHINE
- Doses of enteral or subcutaneous morphine used for the management of breathlessness are generally 25 – 50% of analgesic doses
- Included in EMLc as an analgesic; preparations oral liquid 10mg/5ml; tablets 10mg; s/r tablets 10mg, 30mg, 60mg; injection 10mg/ml
- Widely regarded as first line opioid of choice in severe pain
- Extensive experience of use in the paediatric population
- Readily available worldwide
- Cheap
- Available in oral, rectal and parenteral formulations
- Promotion of single strong opioid may ensure improved use in a number of situations (rather than giving choice)

FENTANYL IN THE MANAGEMENT OF BREATHLESSNESS (DYSPNOEA)

Recommendations
Insufficient evidence to recommend use of nebulised or oral transmucosal fentanyl in the management of breathlessness in adults or children in preference to morphine. Evidence limited to isolated case reports [79] [80] [81]

Evidence for management of this symptom with this drug in children
No evidence to support use of fentanyl in the management of breathlessness in children

Additional supporting information for this drug
None submitted as fentanyl unlikely to be included in the EMLc for this indication

BENZODIAZEPINES IN THE MANAGEMENT OF BREATHLESSNESS (DYSPNOEA)

Recommendations
Benzodiazepines may be used in combination with opioids to control the anxiety associated with dyspnoea although evidence is relatively weak [84] [85] [86] [87]
No evidence of improved efficacy of one benzodiazepine over another. Choice dependent on route of administration, available formulations and clinical preference – lorazepam, diazepam, midazolam

Evidence for management of this symptom with this drug in children
The evidence for effectiveness of benzodiazepines management of anxiety associated with breathlessness in children is limited to case reports, expert opinion and data extrapolated from adults.

Where this alone is insufficient: evidence for management of this symptom in adults
- A randomized controlled trial of 101 adults with advanced cancer suggested that a combination of regular morphine and midazolam was superior to either drug alone in the management of dyspnoea but the results failed to reach statistical significance [85]
- Small randomized controlled studies in breathlessness in adults with COPD have failed to show conclusive benefit from benzodiazepines in the reduction of dyspnoea

Additional supporting information for benzodiazepines
- No evidence of improved efficacy of one benzodiazepine over another was identified.
- The choice(s) of benzodiazepine for inclusion in the EMLc is therefore likely to be determined by availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.
- Lorazepam may be preferred to diazepam for treating acute attacks because of the rapid onset of effect when administered sublingually and it also tends to cause less sedation.
- Diazepam may be more appropriate for chronic anxiety-related dyspnoea symptoms because of its medium to long half life.
- Midazolam injection can be administered bucally if rapid onset is required.
- A continuous SC infusion of midazolam may be of use in the last few days or hours of life.
- Midazolam can be used for intractable breathlessness when required or by continuous subcutaneous infusion to relieve symptoms. Its main advantage is that it is water soluble with most of the drugs commonly given by continuous subcutaneous infusion.

Additional supporting information & comparative data for benzodiazepines

	Route of administration	Formulations	Licensed status in UK, USA and Australia	Current inclusion in EMLc or EML	Pharmacology / Pharmacokinetics	Cost	Other potential roles in palliative care
Diazepam	Oral Rectal Parenteral (IV only)	Oral tablets Oral liquid Injection Rectal tubes	All ages – sedation; pre-med; acute muscle spasm; convulsions; acute anxiety/agitation	Injection 5mg/ml and oral tablets 5mg as pre-operative medication and sedation for short procedures and as an anticonvulsant	**Injection not suitable for SC administration** Wide therapeutic index (wide margin of safety against toxicity) **High oral bioavailability (~100%)** Onset of action following oral administration ~15 mins **Plasma half life 20-100 hours; active metabolite nordiazepam 30-200 hours** Duration of effect 3-30 hours (slow / fast metabolisers)	Oral @ 2-10mg/day ~ 4-20p/day Rectal @ single dose of 5mg ~ £1.30	Adjunct analgesic in smooth muscle spasm Convulsions
Midazolam	Parenteral (SC or IV) Injection may be administered by buccal or oral routes (unlicensed)	Injection	All ages - sedation	No	**Not readily available as an oral or buccal formulation but the injection solution can be administered by these routes** Midazolam injection is highly water soluble enabling administration by SC injection and infusion **Midazolam is compatible with most of the drugs commonly administered by SC syringe driver** In single doses for sedation, midazolam is 3x as potent as diazepam; as an anticonvulsant it is 2x as potent. With multiple doses, diazepam gains potency due to its prolonged half-life **Buccal bioavailability ~75%; oral bioavailability ~45%** Onset of action: SC 5-10 mins; oral 60 mins; buccal within 15 minutes **Short acting with plasma half life 2-5 hours (extended by continuous SC infusion to ~10 hours)**	SC infusion @ 15-30mg/day ~ 90p - £1.80/day	As a parenteral benzodiazepine in muscle tension/spasm; terminal agitation; convulsions
Lorazepam	Oral Parenteral (IV)	Oral tablets Oral liquid (some countries) Injection	All ages – status epilepticus; Anxiety: – oral from 5 years in UK and 12 years in USA, injection from 12 years in UK and 18 years in USA	No	**Injection not recommended for SC administration** Injection can be administered by the sublingual route **Oral bioavailability ~93%** Onset of action 5 mins SL and 10-15 mins orally **Plasma half-life much shorter than diazepam (12-15 hours) but duration of effect does not correlate with plasma concentrations and can be longer (upto 72 hours)**	Oral @ 2-6mg/day ~ 40p - £1.20/day IV infusion @ 4-12mg/day ~ 40p - £1.20/day	Convulsions

STRONG OPIOIDS IN PALLIATION OF BREATHLESSNESS (DYSPNOEA) IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
72	Jennings AL et al. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database of Systematic Reviews 2001	Systematic review	Double blind placebo controlled or crossover RCTs of opioid drugs in relieving breathlessness in patients receiving palliative care for malignancy or other advanced disease	▪ 18 trials identified: oral/parenteral (n=9) and nebulised (n=9) ▪ All 9 nebulised trials were of morphine and 3 of the oral/parenteral trials were morphine ▪ Statistically strong evidence for a small and probably clinically significant effect of oral and parenteral opioids ▪ No evidence that nebulised opioids are more effective than placebo	All but one of the studies identified were small (8 and 18 subjects). Many of the studies included were over 10 years old and used drugs that are less commonly prescribed today.	1++
73	Viola R et al. The management of dyspnea in cancer patients: a systematic review. Support Care Cancer, 2008; 16: 329-337	Systematic review	3 systematic reviews (1 with meta-analysis), 2 practice guidelines and 28 controlled trials identified Adult patients with advanced cancer or other chronic condition and dyspnoea treated with opioids, benzodiazepines, phenothiazines or corticosteroids	▪ Results of individual trials mixed but systematic review with meta-analysis showed a significant benefit for dyspnoea with systemic opioids ▪ Nebulised morphine was not effective in controlling dyspnoea ▪ In ten trials of systemic opioids in other patient populations, there were mixed results	Adult patients with advanced cancer and dyspnoea. Review of the following pharmacological therapies: opioids, benzodiazepines, phenothiazines and systemic corticosteroids. Three studies evaluated morphine and 4 dihydrocodeine	1+
74	Brown SJ et al. Nebulised morphine for relief of dyspnoea due to chronic lung disease. Ann Pharmacother, 2005; 39: 1088-92	Systematic review	Further in-depth review of the 9 nebulised studies included in the Cochrane review above	▪ 9 trials identified ▪ 3 had positive results, rest failed to show any improvement	Small number of subjects, variety of disease states and doses of nebulised morphine and different outcome measures limit interpretation of the studies.	1++
75	Abernethy AP et al. Randomised, double-blind, placebo-controlled trial of sustained release morphine for the management of refractory dyspnoea. BMJ, 2003; 327: 523-526	Randomised, double-blind, placebo-controlled crossover trial	38 adult patients with refractory dyspnoea randomised to sustained release morphine or placebo followed by immediate cross-over to alternative treatment	▪ Participants reported a significantly improved dyspnoea score and better sleep when treated with morphine	Participants generally elderly and poorly functioning No washout period between treatments Constipation reported as a distressing problem with morphine despite use of laxatives	1+

STRONG OPIOIDS IN PALLIATION OF BREATHLESSNESS (DYSPNOEA) IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
76	Allard P et al. How effective are supplementary doses of opioids for dyspnoea in terminally ill cancer patients? A randomised continuous sequential trial. J Pain Symptom Manage 1999; 17(4): 256-265	Randomised continuous sequential clinical trial	33 terminally ill cancer patients with persistent dyspnoea after rest and treatment with oxygen. Patients received 25% or 50% of usual 4H opioid dose	▪ In both groups dyspnoea intensity and respiratory frequency decreased significantly relative to baseline ▪ No difference between groups therefore no obvious advantage in using more than 25% of regular opioid dose ▪ Beneficial effect may extend for as long as 4 hours		2+
77	Cohen SP et al. Nebulised morphine as a treatment for dyspnoea in a child with cystic fibrosis. Pediatrics 2002; 110(3): e38	Case report	Single patient of 10 years given nebulised morphine for control of chest pain and dyspnoea	▪ Mild beneficial effect		3
78	Robinson WM et al. End-of-life care in cystic fibrosis. Pediatrics, 1997; 100(2): 205-209	Retrospective case series	44 patients aged 5 years and over who died of CF-related respiratory failure	▪ 86% of these patients had received oral or parenteral opioids for severe dyspnoea and pain. Use of opioids appeared to be effective in management of dyspnoea.		3
79	Coyne PJ et al. Nebulised fentanyl citrate improves patients' perception of breathing, respiratory rate and oxygen saturation in dyspnoea. J Pain and Symptom Manage 2002; 23(2): 157-160	Case series	32 adult patients with cancer and dyspnoea treated with nebulised fentanyl	▪ 81% patients had a subjective improvement		2-
80	Graff GR et al. Nebulised fentanyl for palliation of dyspnoea in a cystic fibrosis patient. Respiration, 2004; 71: 646-649	Single case report	17 year old patient with end-stage cystic fibrosis	▪ Some improvement in symptoms		3
81	Benitez-Rosario MA et al. Oral transmucosal fentanyl citrate in the management of dyspnoea crises in cancer patients. J Pain and Symptom Manage, 2005; 30(5): 395-397	Case reports	4 adult patients with terminal cancer	▪ OTFC improved dyspnoea in all 4 cases		3
82	CKS – Palliative Care – Dyspnoea 2007	Consensus guideline based on literature review and expert opinion			▪ Supports use of systemic opioids	4
83	Clemens KE, Klaschik E. Symptomatic therapy of dyspnoea with strong opioids and its effect on ventilation in palliative care patients. J Pain Symptom Manage 2007; 33(4): 473-81	Prospective non-randomized, uncontrolled trial	11 adult patients with dyspnoea admitted to a palliative care unit	▪ A significant reduction in dyspnoea was observed with administration of enteral opioids but not with administration of oxygen ▪ Reduction in respiratory rate was associated with reduction in dyspnoea ▪ Other monitored respiratory parameters including oxygen saturation, transcutaneous aterial carbon dioxide pressure and pulse rate did not change		

BENZODIAZEPINES IN THE PALLIATION OF BREATHLESSNESS (DYSPNOEA) IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comments**	**Grade of Evidence**
84	Viola R et al. The management of dyspnea in cancer patients: a systematic review. Support Care Cancer, 2008; 16: 329-337	Systematic review	Studies identified for benzodiazepines, Navigante AH et al (as below) and 4 crossover trials in non cancer patients	▪ Randomised trial by Navigante below which detected an improvement in dyspnoea intensity from baseline with morphine, with midazolam and a combination of the two but no between-treatment differences ▪ Four crossover-trials in noncancer patients compared a benzodiazepine with placebo and one included a phenothiazine arm. Of these, one was of poor quality and excluded and of the remaining 3, none detected a significant reduction in dyspnoea after treatment with a benzodiazepine compared to placebo	▪ Controlled trials of benzodiazepines in non-cancer patients did not show any benefit for treating dyspnoea ▪ In a single-blind trial involving cancer patients, reduction in dyspnoea intensity was not significantly different with SC midazolam, administered with or without morphine, compared with SC morphine alone	1+
85	Navigante AH et al. Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnoea perception in patients with advanced cancer. J Pain Symptom Manage, 2006; 31(1): 38-47	Randomised trial	101 adult cancer patients assigned to 1 of 3 treatment groups (regular morphine with midazolam rescue doses; regular midazolam with morphine rescue doses; regular morphine and midazolam with morphine rescue doses). All drugs given SC	▪ Dyspnoea better controlled with fewer breakthrough episodes in the group treated with regular morphine and midazolam		1-
86	CKS – Palliative Care – Dyspnoea 2007	Consensus guideline based on literature review and expert opinion			▪ Supports use of benzodiazepines	4
87	Twycross and Wilcock. Symptom Management in Advanced Cancer. 3rd Edition	Expert opinion				4

Nausea and vomiting

Recommendations for Inclusion: HALOPERIDOL, CYCLIZINE, METOCLOPRAMIDE, LEVOMEPROMAZINE,

New medicines for addition to EMLc: Cyclizine and Levomepromazine

New formulations for addition to EMLc:
Cyclizine oral tablets 50mg and injection 50mg/ml
Levomepromazine oral tablets 25mg and injection 25mg/ml

DEFINITION

- Nausea is the unpleasant sensation of needing to vomit.
- Vomiting is the forceful expulsion of gastric contents through the mouth.
- Although nausea and vomiting often occur together they are in fact separate symptoms

SCOPE

- Management of nausea and vomiting comprises identification and wherever possible treatment of possible underlying cause(s)
- Most cancer chemotherapy is highly emetogenic. Appropriate management of chemotherapy induced nausea and vomiting depends on the chemotherapy regime.
- Mechanisms of post-operative nausea and vomiting are likely to be different to nausea and vomiting in palliative care
- The scope of EMLc palliative care does not include management of chemotherapy induced or post-operative nausea and vomiting
- Management of nausea and vomiting should not be deferred until the underlying cause of the nausea and vomiting has been identified but treatment of nausea and vomiting identification and if appropriate treatment of the underlying cause should be undertaken simultaneously.
- Pharmacological management is the mainstay of treatment of nausea and vomiting, however non pharmacological measures including avoidance of precipitants and the use of acupressure may have a role. Here we consider only pharmacological measures

OVERVIEW OF MANAGEMENT OPTIONS

- Pharmacological management based on knowledge of the most important pathophysiological mechanisms for emetogenesis and the relevant neurotransmitters is suggested for optimum management of nausea and vomiting [98, 101] but the evidence to support this approach has been questioned [88].
- Unfortunately it is not always possible to identify the precise mechanism(s) underlying the presence of nausea and vomiting in many children. A pragmatic approach addressing the most likely mechanism is indicated.
- Antiemetics should be prescribed regularly and as required.
- If a single first line antiemetic does not relieve nausea and vomiting the antiemetic regime should be reviewed to ensure that
    - The likely pathophysiological mechanisms underlying nausea and vomiting are being targeted
    - The child is receiving the medication and that it is being absorbed
    - The dose is appropriate
- If necessary a second antiemetic with a complementary mechanism of action may be added

- Combinations of antiemetics with antagonistic actions should be avoided
- Alternatively the first line antiemetic can be changed to a single second line antiemetic with a more appropriate or broader spectrum of action
- Where the enteral route is unavailable or absorption is not reliable an alternative route of administration, either rectal or subcutaneous (or intravenous if long term central venous access is available) is required
- Antiemetic administration via continous subcutaneous (or intravenous if long term central venous access is available) infusion is the route of choice where the enteral and rectal routes are unavailable and regular dosing is required

CLASSE(S) OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

- Typical antipsychotics
    - Haloperidol, Levomepromazine, chlorpromazine, prochlorperazine
- Antiemetic antihistamines
    - Cyclizine, promethazine
- 5HT3 antagonists
    - Ondansetron
- Corticosteroids
    - Dexamethasone
- Prokinetic antiemetics
    - Metoclopramide, domperidone

ANTIEMETICS IN PALLIATIVE CARE

Recommendations
Evidence base for pharmacological treatment of nausea and vomiting in palliative and terminal care is weak [88]
If cause of emesis established, choice of first line agent should correlate with this cause [88] [89] [91] [95] [96] [97] [99] [100]
For effective control, a combination of anti-emetics with complementary actions may be necessary

Evidence for management of this symptom in children

- Evidence to support the use of anti-emetics in children is almost exclusively limited to post-operative nausea and vomiting or nausea and vomiting associated with cancer chemotherapy.
- Evidence to support the use of antiemetics in nausea and vomiting in palliative care is limited to case reports, expert opinion and extrapolated data from adults

Where this alone is inadequate evidence for management of this symptom in adults

- The evidence base for the pharmacological treatment of nausea and vomiting in palliative care in adults is weak and based largely on clinical experience and proven efficacy of these agents in other situations.
- Availability of a combination of antiemetics with different mechanisms of action is recommended to ensure appropriate first and second line management for each underlying pathophysiological mechanism
- In the absence of any data showing greater efficacy of one agent over another, the choice of antiemetics within a class for inclusion in the EMLc likely to be determined by other factors such as availability of suitable formulations, route of administration, pharmacokinetics, cost-effectiveness and potential for other roles in palliative care

Mechanism of action	Aetiology	Pharmacological management
Chemical trigger zone (CTZ) stimulation D2, 5HT3 receptors	*Chemicals*: ▪ Drugs (eg. Opioids, metronidazole) ▪ Metabolites (hypercalcaemia, uraemia) ▪ Toxins	**Haloperidol** ▪ Blocks D2 receptors ▪ Once daily, low dose required ▪ Caution in movement disorders ▪ Contraindicated with metoclopramide or levomepromazine **Levomepromazine** ▪ (2nd line – stop haloperidol) ▪ Low dose
Vomiting centre (VC) stimulation H1, AChm, 5HT2 receptors	*Autonomic afferents*: • Stretch receptors in serosae and viscera • Irritated GI mucosa: drugs, infection, RXT *Direct stimulation*: ▪ Head & neck radiotherapy ▪ Brainstem metastases ▪ Raised intracranial pressure	**Cyclizine** ▪ Blocks H1 and AChm receptors Levomepromazine ▪ (2^{nd} line – stop cyclizine) ▪ Low dose
Higher centre stimulation 5HT GABA receptors	▪ Pain ▪ Fear ▪ Anxiety ▪ Memory	**First line management with non-pharmacological interventions** **Benzodiazepines** ▪ (2^{nd} line) ▪ Midazolam
Mechanical causes **Gastric stasis** May not be mediated by VC (less nausea)	• Reduced motility from drugs (amitriptyline, hyoscine, opioids) • Local tumour causing (partial) outflow obstruction	**Metoclopramide** ▪ Blocks D2 and stimulates 5HT4 receptors

Additional supporting information for these drugs

HALOPERIDOL

- Haloperidol is a powerful D2 receptor antagonist and has antiemetic properties with actions on the area postrema.
- Haloperidol is recommended for the first line management of nausea and vomiting due to drug induced or metabolic causes.
- Haloperidol is already included in the EMLc as an antipsychotic.
- Haloperidol can be administered subcutaneously or intravenously as a continuous infusion with other medication for symptom management when the enteral route is no longer available.

CYCLIZINE

- Cyclizine is an antihistaminic anti-muscarinic anti-emetic.
- It is considerably less sedating than diphenhydramine.
- It has a similar spectrum of action to promethazine but is considerably less sedating. Sedation associated with promethazine has been associated with the sudden infant death syndrome
- Cyclizine is an antihistamine and, unlike promethazine which is a phenothiazine, can be used safely in combination with haloperidol.

- Cyclizine can be administered subcutaneously or intravenously as a continuous infusion with other medication for symptom management when the enteral route is no longer available.
- The inclusion of cyclizine is recommended for the first line management of nausea and vomiting due to stimulation of the vomiting centre due to raised intracranial pressure, efferent activity from stretch receptors in serosa of viscera or gastrointestinal mucosal irritation.

METOCLOPRAMIDE

- Metoclopramide is a prokinetic antiemetic already included in EMLc.
- Metoclopramide is recommended for the first line management of nausea and vomiting associated with delayed gastric emptying.

LEVOMEPROMAZINE

- Levomepromazine has potent broad spectrum antiemetic properties and is less sedating than chlorpromazine at equivalent antiemetic doses.
- There is considerable experience of the use of levomepromazine in management of nausea and vomiting refractory to first line treatment in adult palliative care patients and to a lesser extent in paediatric palliative care.
- Levomepromazine can be administered subcutaneously and as a continuous infusion with other medication for symptom management when the enteral route is no longer available.

Additional supporting information /comparative data for antiemetics

	Main site of action / receptors	Routes of administration	Available formulations	Licensed status in UK, USA, Australia	Current listing in EMLc or EML	Pharmacology / Pharmacokinetics	Cost	Other potential roles in palliative care
Haloperidol	Potent D2 receptor antagonist Area postrema	Oral Parenteral	Oral tablets/capsules Oral liquid Injection	Oral: all ages for behavioural disorders Injection: not licensed in children	EMLc and EML – psychotic disorders	**No antimuscarinic properties** Can cause extrapyramidal side effects **Oral bioavailability 60-70%** Onset of action: 10-15 mins SC; >1 hour oral **Duration of effect: up to 24 hours**	Oral: 1.5mg once or twice daily 9-18p/day IV or SC infusion: 1.5mg over 24 hours 30p/day	Confusion/ delirium; agitation
Metoclopramide	D2-receptor antagonist and 5HT4 receptor agonist Prokinetic in GI tract	Oral Parenteral	Oral tablets Oral liquid Injection	Oral and parenteral: all ages for nausea and vomiting	EMLc and EML - antiemetic	**Action antagonised by antimuscarinics** Can cause extrapyramidal side effects **Oral bioavailability: 50-80%** Duration of action following single dose: 1-2 hours	Oral: 5mg/dose TDS ~10p/day IV: 5mg/dose TDS ~ 75p/day	None
Domperidone	D2-receptor antagonist Prokinetic in GI tract	Oral Rectal	Oral tablets Oral liquid Suppositories	UK Oral and rectal: > 2 years ? availability in USA and Australia	No	**Does not cross BBB** Does not cause extrapyramidal side effects **Action antagonised by antimuscarinics** Onset of action ~ 30 minutes **Duration of action: 8-16 hours**	Oral: 5-10mg/dose TDS ~10p/day Rectal: 30mg/dose BD ~ 65p/day	None
Cyclizine	Moderate histamine (H1-receptor)/ muscarinic antagonist. Acts on vomiting centre	Oral Parenteral	Oral tablets Injection	UK: from 6 years of age Does not appear to be readily available or used in USA or Australia	No	**Less drowsiness than promethazine** Onset of action: ~ 30 mins with maximal effects after 1-2 hours **Duration of action 4-6 hours (shorter acting than promethazine)** More IV compatibility data than promethazine	Oral / IV: 25mg/dose TDS Oral ~ 20p/day; IV ~ £1.60/day	None
Promethazine	Potent histamine (H1-receptor)/ muscarinic antagonist Acts on vomiting centre	Oral Parenteral Rectal (in some countries)	Oral tablets Oral liquid Injection Rectal suppositories	From 2 years of age as an antiemetic and antihistamine	EMLc and EML as an antiemetic	**Long acting antihistamine; elimination half-life 7-15 hours** Can cause respiratory depression and sedation. **Caution under 2 years**	Oral: 5-10mg/dose BD ~ 7p/day IV: 12.5mg/dose QDS ~ £2/day	None

	Main site of action / receptors	Routes of administration	Formulations	Licensed status in UK, USA, Australia	Current listing in EMLc or EML	Pharmacology / Pharmacokinetics	Cost	Other potential roles in palliative care
Chlorpromazine	Moderate D2 receptor antagonist, H1-receptor antagonist and slight antimuscarinic activity Acts on vomiting centre	Oral Parenteral (IM)	Oral tablets Oral liquid Injection (IM)	From 6 months of age as an antiemetic and as an neuroleptic	EMLc and EML – psychotic disorders	**Can cause extrapyramidal side effects** Oral bioavailability: 30-50% Peak plasma concentration **Duration of effect from single dose ~ 24 hours**	Oral: max 40mg/day ~12p/day	Confusion/ delirium; agitation
Levomepromazine	Potent H1- and 5HT2 receptor antagonist; moderate D2 and muscarinic antagonist Broad spectrum agent acting in vomiting centre	Oral Parenteral	Oral tablets Injection	UK – lower age limit unclear but licensed for use in terminally ill children as an antiemetic, analgesic and for restlessness and distress No longer available in USA	No	**Can cause extrapyramidal side effects** May cause more sedation than chlorpromazine **Onset of action ~ 30 mins** Duration of action 12-24 hours	Oral: 6.25mg/dose TDS ~50p/day IV or SC infusion: 5mg over 24 hours ~ £2.00/day	Agitation Pain
Ondansetron	5HT3 antagonist acting in GI tract and area postrema	Oral Rectal Parenteral	Oral tablets Oral liquid Oral melts Rectal suppositories Injection	All ages for emesis associated with chemotherapy; from 2-4 years for PONV	No	**More often used in management of N+V associated with chemotherapy** Onset of action: orally < 30 mins; IV < 5 mins **Duration of action ~ 12 hours**	Oral: 4mg/dose TDS ~£10/day IV: 4mg/dose TDS ~ £18/day	None
Dexamethasone	Anti-inflammatory	Oral Parenteral	Oral tablets Oral liquid Injection	All ages for a variety of conditions	EMLc and EML (injection only) – allergy or anaphylaxis	**High glucocorticoid activity but insignificant mineralocorticoid effect; suitable for high dose therapy** Biological half life 36-54 hours	Oral: @ 12mg/day ~ £1.40/day IV: @12mg/day ~£2.50/day	Adjunct analgesic in pain Anorexia Fatigue
Hysocine butylbromide	Antimuscarinic (antisecretory) in GI tract	Oral Parenteral	Oral tablets Injection	UK: oral from 6 years for GI or GU muscle spasm; injection not licensed in children This salt of hyoscine does not appear to be used in USA	No	**Quaternary amine** Does not cross BBB and so does not have a central anti-emetic action or cause drowsiness **Onset of action following parenteral administration <10 mins** Duration of action <2 hours following single dose	IV Injection: 5-10mg 3-4x daily ~ 60-80p/day	Control of excess respiratory secretions

	Main site of action / receptors	Routes of administration	Formulations	Licensed status in UK, USA, Australia	Current listing in EMLc or EML	Pharmacology / Pharmacokinetics	Cost	Other potential roles in palliative care
Hyoscine hydrobromide	Potent antimuscarinic acting in vomiting centre	Oral Transdermal Parenteral	Oral tablets Transdermal patches Injection	UK: oral from 3 years and patches from 10 years for motion sickness; injection as a pre-med all ages	No	**Tertiary amine** Crosses BBB so has a central action **Can cause sedation (which may be desirable) or agitation that may not** Following single SC dose, short duration of action <1 hour but longer duration of effect with repeat injections	Oral: 150microg dose TDS ~ 35p/day Transdermal: 1 patch every 3 days ~ £2.15 every 3 days SC/IV: @ 1200microg day ~£6.00/day	Control of excess respiratory secretions

ANTIEMETICS IN THE TREATMENT OF NAUSEA AND VOMITING IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
88	Glare P et al. Systematic review of the efficacy of antiemetics in the treatment of nausea in patients with far-advanced cancer. Support Care Cancer 2004; 12: 432-440	Systematic review of studies of antiemetics used in the treatment of advanced cancer	21 studies included of which 2 were systematic reviews, 7 were RCTs, 12 were uncontrolled studies or case series. Only adult studies identified	▪ Evidence base for the pharmacological treatment of nausea and vomiting in advanced cancer is weak and contradictory ▪ Response rates to antiemetic treatment were lower in controlled studies than in the uncontrolled studies ▪ Two possible approaches (a) mechanistic approach which attempts to correlate choice of antiemetic with suspected underlying cause (b) empirical approach in which various antiemetics are trialled without regard to the underlying cause of the nausea ▪ Metoclopramide appears to be more effective than placebo ▪ Little evidence from well designed studies for other widely used antiemetics such as haloperidol, cyclizine and methotrimeprazine ▪ Used empirically, steroids have been used as adjuvants in patients with nausea not responding to other therapy although results are conflicting ▪ Good evidence for the effectiveness of steroids in symptomatic bowel obstruction ▪ Two RCTs indicate the effectiveness of 5HT3 antagonists in palliative care		1+
89	Stephenson J et al. An assessment of aetiology-based guidelines for the management of nausea and vomiting in patients with advanced cancer. Support Care Cancer, 2006; 14: 348-353	Prospective study	121 patients with advanced cancer aged 16 years or over. Those with nausea and vomiting were assessed with the aim of determining the likely cause of vomiting. Once cause established, antiemetics were prescribed according to aetiology-based guidelines	▪ 61 patients had nausea and vomiting during their hospice admission ▪ Only 32 patients evaluable at week 1 ▪ At week 1, 8% were on no antiemetics, 49% on a single agent, 33% on 2 agents and 10% on 3 agents. ▪ Vomiting was controlled in 69% patients at 48H and 89% patients at 1 week ▪ Nausea was controlled in 44% patients at 48H and 56% patients at 1 week ▪ During course of assessment period, physicians altered their opinion about the primary course of N+V in 26% patients and finally expressed confidence about the aetiology in 75% patients	▪ An approach using aetiology-based guidelines in management of N+V is moderately effective although some patients refractory to standard antiemetic regimens ▪ Study would have been strengthened by presence of a control group ▪ Sample sizes small with only 32 of original 61 patients evaluable at week 1 (16 deaths; 9 discharged due to improved symptoms; 4 too unwell to complete assessments)	2-

ANTIEMETICS IN THE TREATMENT OF NAUSEA AND VOMITING IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
90	Lichter I. Results of antiemetic management in terminal illness. J Palliative Care, 1993; 9(2): 19-21	Prospective study of 100 consecutive episodes of nausea and vomiting in terminally ill adults.	100 episodes in 86 patients. Cause established as accurately as possible and choice of initial antiemetic targeted to this cause. Response to antiemetic recorded after 24 hours and if nausea or vomiting persisted, cause reassessed (dose of antiemetic increased, additional or alternative antiemetic chosen). Control assessed again after 48 hours	▪ 70% nausea and vomiting episodes controlled within 24 hours ▪ In 10% patients, episodes controlled within 48 hours by increasing dose of chosen antiemetic ▪ In 12% patients, episodes controlled within 48 hours by addition of another antiemetic ▪ In 1% patients, episodes controlled within 48 hours by change of antiemetic ▪ In total therefore, control of episodes of nausea and vomiting achieved in 93% patients within 48 hours ▪ 17% patients on 2 antiemetics during study ▪ 12% patients in 3 antiemetics during study	▪ Not a controlled study ▪ Suggests nausea and vomiting in terminal illness can be controlled rapidly, in most cases, when antiemetic(s) chosen target the cause(s)	2-
91	CKS – Palliative cancer care-nausea and vomiting	Consensus guideline based on literature review and expert opinion	Assessment and management of nausea and vomiting in patients of 16 years and over in palliative care	▪ **Drug induced or metabolic causes** – haloperidol ▪ **Intracranial disease** – cyclizine (with dexamethasone if intracranial pressure raised) ▪ **Vestibular disorder** – cyclizine ▪ **Peristaltic failure or gastric stasis** – metoclopramide or domperidone ▪ **Mechanical bowel obstruction** – cyclizine (if symptoms persist add haloperidol or levomepromazine). For colic and large-volume vomiting hyoscine butylbromide or octreotide ▪ **Abdominal or pelvic tumour** - cyclizine ▪ **Anxiety-related** - benzodiazepine		4

ANTIEMETICS IN THE TREATMENT OF NAUSEA AND VOMITING IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
92	Meyer M. Palliative care and AIDS. Gastrointestinal symptoms. Int J STD and AIDS, 1999; 10: 495-507	General review article		▪ Generally the initial choice of an anti-emetic lies between 3 drugs, haloperidol, cyclizine and metoclopramide ▪ **Chemoreceptor trigger zone** – haloperidol and phenothiazines are potent D2-receptor antagonists blocking CTZ stimulation. Metoclopramide and domperidone both have some D2-receptor antagonist properties. ▪ **Vomiting centre** – cyclizine acts at the vomiting centre. Levomepromazine, a phenothiazine with antagonistic properties to many vomiting centre and CTZ receptors is a broad spectrum anti-emetic. Can be used as a multi-purpose anti-emetic though it may not be the most effective for a specific cause and it is commonly used as a 2nd or 3rd line anti-emetic when more specific drugs have not been effective. ▪ **Gastrointestinal tract**. Metoclopramide has both D2-receptor antagonist and 5HT4-receptor agonist properties. Acts peripherally on the gut and also has central CTZ anti-emetic action. Prokinetic effect of domperidone is limited to D2-receptor antagonist activity. Other possibilities are 5HT3 receptor antagonists which act peripherally in the gut and centrally in the brain ▪ **Colic / obstruction** – cyclizine and haloperidol act centrally to relieve nausea and vomiting associated with intestinal obstruction. Hyoscine butylbromide may be of use in reducing intestinal motility. Octreotide may be useful adjunctive therapy by inhibiting gut peristalsis from stomach to large bowel and reducing the volume of GI secretions ▪ **Vestibular centre** – contains muscarinic cholinergic and H1 histamine neurotransmitters. Hyoscine hydrobromide or cyclizine ▪ **Cerebral cortex** – to control effects psychological and emotional distress use of benzodiazepines, diazepam or lorazepam ▪ **Others** – corticosteroids. Dexamethasone reduces cerebral and meningeal oedema, is thought to have an anti-tumour effect and has a central anti-emetic effect though its precise site of action is unknown		4
93	Santucci G et al. Common gastrointestinal symptoms in pediatric palliative care: nausea, vomiting constipation, anorexia, cachexia. Pediatr Clin North Am, 2007; 54: 673-689	General review article		▪ Includes some drug choices and doses		4

ANTIEMETICS IN THE TREATMENT OF NAUSEA AND VOMITING IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
94	Bentley A et al. Use of clinical pictures in the management of nausea and vomiting: a prospective audit. Palliative Med, 2001; 15: 247-253	Prospective audit to evaluate a guideline for the management of nausea and vomiting in palliative care inpatients	40 adult patient episodes	▪ 9 drugs were used to control nausea and vomiting: metoclopramide, haloperidol, levomepromazine, cyclizine, domperidone, octreotide, hyoscine butylbromide, cisapride and dexamethasone which are all included in the guidelines ▪ Most common causes gastric stasis/obstruction (first line metoclopramide) and chemical/metabolic (first line haloperidol)		3
95	Cancer Care Alliance, UK. Network Supportive and Palliative Care Guidelines, 2006	Guidelines	?Adult patients	▪ **Metabolic** – haloperidol, levomepromazine ▪ **Gastric stasis** – metoclopramide, domperidone; consider trial of steroids ▪ **GI disturbance and/or organ damage** – cyclizine ▪ **Bowel obstruction** – Consider trial of steroids; consider metoclopramide if no colic. High bowel obstruction – cyclizine and haloperidol. Low bowel obstruction – levomepromazine; consider hyoscine butylbromide or octreotide for anti-secretory effects ▪ **Raised ICP** – cyclizine (consider steroids if raised ICP) ▪ **Psychological factors** – levomepromazine, benzodiazepine ▪ **Cause unknown/terminal** - levomepromazine		4
96	Baines MJ. ABC of palliative care: nausea, vomiting and intestinal obstruction. BMJ, 1997; 315: 1148-50	General review article		▪ **Opioid induced** – metoclopramide or haloperidol ▪ **Renal failure** – haloperidol (levomepromazine sometimes required) ▪ **Functional gastric stasis** – metoclopramide or domperidone ▪ **Inoperable GI obstruction** – metoclopramide +/- dexamethasone. Octreotide or high dose hyoscine butylbromide may reduce the volume of vomit ▪ **Raised ICP** – dexamethasone or cyclizine ▪ **Vestibular disturbance** - cyclizine		4
97	Twycross and Wilcock. Symptom management in advanced cancer. 3rd Edition	Expert opinion		▪ **Prokinetic anti-emetic** - metoclopramide ▪ **Chemoreceptor trigger zone** – haloperidol ▪ **Antispasmodic and anti-secretory** – hyoscine butylbromide ▪ **Vomiting centre** – cyclizine (in combination with dexamethasone if raised ICP) ▪ **Broad-spectrum antiemetic** – levomepromazine ▪ **Others –** corticosteroids ; 5-HT3 receptor antagonists, octreotide		4
98	Mannix K. Palliation of nausea and vomiting in malignancy. Clin Med 2006; 6(2): 144-7	General review article		▪	**Supports the phat**	

ANTIEMETICS IN THE TREATMENT OF NAUSEA AND VOMITING IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
99	Regnard and Hockley. A guide to symptom relief in palliative care. 5th Edition	Expert opinion		▪ Four key antiemetics – cyclizine, haloperidol, metoclopramide (or domperidone in children) and levomepromazine.		4
100	Jassal SS et al. Basic Symptom Control in Pediatric Palliative Care – The Rainbows Children's Hospice Guidelines 2008	Expert opinion		▪ Possible choices – haloperidol, thioridazine, chlorpromazine, prochlorperazine, ondansetron, cyclizine, levomepromazine, domperidone, metoclopramide, dexamethasone		4
101	Bentley A and Boyd K. Use of clinical pictures in the management of nausea and vomiting: a prospective audit. Palliative Med 2001; 15: 247-253	Prospective uncontrolled study evaluating the implementation of nausea and vomiting according to a guideline based on the clinical picture and likely underlying pathophysiological mechanism	40 episodes of vomiting in palliative care inpatient setting	▪ Commonest clinical pictures were gastric stasis/ outlet obstruction (35%) and chemical/ metabolic (30%) ▪ Management according to the guideline appeared effective with nausea abolished in 82% cases and vomiting abolished completely in 84% cases ▪ Symptoms were completely controlled in a mean time of 3.4 days		

HALOPERIDOL AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
102	Critchley P et al. Efficacy of haloperidol in the treatment of nausea and vomiting in the palliative patient: a systematic review. J Pain Symptom Manage, 2001; 22(2): 631-633	Systematic review	6 studies of which 4 were case series and 2 were case reports. Patients of any age could be included.	▪ Case series of 22 cancer patients with inoperable GI obstruction of whom 15 reported vomiting. SC or IV haloperidol controlled the vomiting in 12 of these patients ▪ Case series of 25 adult cancer patients with bowel obstruction and who were treated with a combination of medications including IM, SC or sublingual haloperidol. ▪ Case report suggesting that combined blockade of dopamine and serotonin receptors in the chemoreceptor trigger zone with haloperidol and ondansetron is sometimes required to relieve intractable nausea and vomiting	▪ Only 3 of the 6 studies included in this review provided enough information to suggest that haloperidol may be effective in patients diagnosed with a variety of cancers who experience nausea and vomiting ▪ Review only considered cancer patients ▪ Review shows the lack of well designed and clearly reported studies evaluating the treatment of nausea and vomiting in palliative patients	2++
103	Buttner M et al. Is low-dose haloperidol a useful antiemetic? A meta-analysis of published and unpublished randomised trials. Anesthesiology, 2004; 101: 1454-1463	Meta-analysis	15 published and 8 unpublished randomised trials including 1397 adults who received haloperidol and 1071 controls. 1994 patients with PONV, 261 gastroenterology patients, 189 with chemotherapy, 24 with radiation therapy	▪ IM or IV haloperidol in low doses is effective in PONV and in the control of emesis due to various GI disorders ▪ Evidence less clear for emesis associated with chemotherapy or radiation	▪ No randomised trials on emesis in palliative care identified for inclusion ▪ Trial design of some included studies unsatisfactory ▪ Data on repetitive doses scarce	1+
104	Vella-Brincat J et al. Haloperidol in palliative care. Palliative Med, 2004; 18: 195-201	Review of the clinical indications for haloperidol in palliative care			▪ Nausea and Vomiting – haloperidol acts at dopamine 2 and other receptors in various regions of the brain as an antagonist ▪ Antagonism of dopamine 2 receptors in the chemoreceptor trigger zone resulting in alleviation of nausea and vomiting ▪ Evidence of efficacy of haloperidol as an antiemetic, although based on sound pharmacology, is not substantiated by any randomised controlled trials	4
105	Siden HB. Haloperidol as a palliative anti-emetic in a toddler: an evidence base challenge. J Pain Symptom Manage, 2008; 35(3): 235-238	Case report	16 month old male with relapsed ALL	▪ Abdominal discomfort and nausea and vomiting despite use of ondansetron, dimenhydrinate, clobazam, ranitidine and simethicone ▪ Oral haloperidol 0.07mg/kg/dose 8H via NG tube ▪ Emesis controlled and he became less irritable ▪ No extrapyramidal symptoms or dyskinesias ▪ Infant died within a few days	▪	3

METOCLOPRAMIDE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
106	Bruera E et al. A double-blind crossover study of controlled-release metoclopramide and placebo for the chronic nausea and dyspepsia of advanced cancer. J Pain and Symptom Manage, 2000; 19(6): 427-435	Randomised, double-blind study to compare controlled-release metoclopramide with placebo in mild to moderate nausea	26 adult patients with a 1 month or greater history of cancer-associated dyspepsia syndrome randomised to receive oral controlled release metoclopramide or placebo for 4 days followed by crossover	▪ Only 20 of the 26 patients were evaluable ▪ Nausea significantly lower in active treatment phase ▪ Nausea scores tended to increase across days during the placebo phase and to decrease in the active phase ▪ Frequency of administration of rescue medication to control breakthrough symptoms did not differ overall between active treatment and placebo ▪ Peak rescue administration occurred during daytime in both groups with almost no rescue during night-time ▪ Frequency and severity of adverse events did not differ significantly between groups		1-
107	Bruera E et al. Chronic nausea in advanced cancer patients: a retrospective assessment of a metoclopramide-based antiemetic regimen. J Pain Symptom Manage, 1996; 11(3): 147-53	Review of anti-emetic therapy, to report on the frequency and intensity of chronic nausea in these patients and describe the results of a treatment regime	100 adult patients with terminal cancer and normal cognitive function	▪ Step 1 – oral or SC metoclopramide 10mg every 4H with supplemental doses of 10mg orally every hour as needed ▪ Step 2 – as step 1 with addition of oral or SC dexamethasone 10mg BD ▪ Step 3 – continuous SC infusion of metoclopramide (60-120mg/day) with dexamethasone as in step 2 ▪ Step 4 – alternative antiemetics	▪ On admission to palliative care unit, 32% patients presented with nausea that required treatment although 98% patients developed nausea during admission ▪ 25% patients required other antiemetics because of bowel obstruction, extrapyramidal side-effects or other reasons ▪ Most patients without bowel obstruction achieved excellent control of nausea using the metoclopramide-based regimen at step 1, 2 or 3	3
108	Bruera E et al. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomised controlled trial. J Pain and Symptom Manage, 2004; 28(4): 381-388	Double-blind parallel study	51 patients aged 16 years or over with chronic nausea refractory to metoclopramide. Patients received oral dexamethasone 20mg/day or placebo in addition to oral metoclopramide 60mg/day	▪ 25 patients randomised to dexamethasone, 26 to placebo in addition to metoclopramide ▪ 3/25 dexamethasone patients withdrew because of gastric irritation or uncontrolled N+V; 5 of the 26 placebo patients withdrew ▪ Major improvement in nausea appetite and fatigue on Day 3 and Day 8 in both groups ▪ Pain, vomiting, well-being and quality of life remained unchanged in both groups on Day 3 and Day 8	▪ Dexamethasone was not superior to placebo in the management of chronic nausea in this group of patients with advanced cancer	1+

METOCLOPRAMIDE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
109	Wilson J et al. Long-term safety and clinical effectiveness of controlled-release metoclopramide in cancer-associated dyspepsia syndrome: a multicentre evaluation. J Palliative Care, 2002; 18(2): 84-91	3 month open-label evaluation of safety and clinical effectiveness of controlled-release metoclopramide in cancer patients with nausea and other GI symptoms	48 adult patients with a minimum 2-week history of cancer associated GI symptoms were assigned to a single, open-label treatment group and received controlled release metoclopramide for a maximum period of 12 weeks	▪ 33% early terminations (n=16) were due to one or more adverse event ▪ Controlled release metoclopramide was effective in decreasing the severity of nausea in patients with cancer by 40-60% in the first 2 weeks of treatment ▪ Severity of vomiting was also reduced with a 50% decline in the first 4 weeks of treatment	▪ Conclusions limited by open-label nature of the study (although results confirmed in randomised, double-blind placebo-controlled study above (1))	2-
110	Corli O et al. Effectiveness of levosulpiride versus metoclopramide for nausea and vomiting in advanced cancer patients: a double-blind, randomised, crossover study. J Pain Symptom Manage, 1995; 10(7): 521-526	Double-blind, randomised, crossover study	30 adult patients with advanced cancer randomised to receive either levosulpiride or metoclopramide for 7 days. After 7 days, patients were crossed over to the alternate treatment which was also given for 7 days	▪ Both treatments were effective in controlling nausea and vomiting in this patient group ▪ Improvement in nausea over baseline values was significant both with levosulpiride and metoclopramide immediately after the first day of administration ▪ With regard to vomiting, improvement was significant after the first day of treatment with levosulpiride and only after the second day with metoclopramide ▪ Complete control of nausea obtained in 84.6% patients receiving levosulpiride and 42.3% of those treated with metoclopramide ▪ Vomiting disappeared in 81.5% patients receiving levosulpiride and 51.8% those treated with metoclopramide ▪ There was a carry-over effect in favour of levosulpiride	▪ Both levosulpiride and metoclopramide reduce nausea and vomiting in this patient population but levosulpiride is more effective	1+

DOMPERIDONE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
No specific references identified for domperidone in palliative/terminal care or advanced cancer					

CYCLIZINE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
No specific references identified for cyclizine in palliative/terminal care or advanced cancer					

PROMETHAZINE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
No specific references identified for promethazine in palliative/terminal care or advanced cancer					

LEVOMEPROMAZINE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
111	Eisenchlas JH et al. Low dose levomepromazine in refractory emesis in advanced cancer patients: an open label study. Palliative Med, 2005; 19: 71-75	Open label prospective study	70 adult patients with advanced cancer and refractory emesis treated with SC boluses of levomepromazine	▪ Treatment was associated with a decrease in nausea score (numerical rating scale) from a median of 8/10 at baseline to a median of 1 after 2 days of treatment ($p<0.0001$) ▪ Vomiting ceased in 92% cases ▪ All 11 patients who had a nasogastric tube at baseline had it successfully removed 48 hours after starting levomepromazine ▪ Most frequently reported side effect was sedation ▪ Mean daily dose of SC levomepromazine was 6.25mg (range 3.125 – 25mg)	▪ Low dose levomepromazine by SC bolus injection once daily is generally efficacious in patients with advanced cancer and emesis refractory to first-line treatment ▪ Non controlled study – possible placebo effect from drug administration itself ▪ Levomepromazine doses not standardised so not possible to establish effective starting dose	2-
112	Kennett A et al. An open study of methotrimeprazine in the management of nausea and vomiting in patients with advanced cancer. Support Care Cancer, 2004; 13: 715-721	Open study	65 adult patients with advanced malignancy. Given oral or SC methotrimeprazine with initial dose and route dependent on severity of symptoms. Dose was escalated through 3 treatment levels until symptoms were controlled or side effects occurred	▪ At day 2, 53 patients evaluable for response and 33 (62%) showed some improvement in nausea and vomiting. ▪ At day 5, 34 patients evaluable for response. Of these, 12 had a complete response (nausea and vomiting scores of 0) and 8 a partial response (reduction in nausea and vomiting scores from baseline) giving an overall response rate of ~ 58.8% ▪ Most common side effects were drowsiness, dry mouth and loss of concentration ▪ Majority of patients controlled on 'low-dose' methotrimeprazine (12.5mg oral daily or less)		2-

PROCHLORPERAZINE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
113	Weschules DJ et al. Are newer, more expensive pharmacotherapy options associated with superior symptom control compared to less costly agents used in a collaborative practice setting. Am J Hosp Palliat Care, 2006; 23: 135-149	Retrospective with a cohort	Adult hospice patients. In treatment of nausea, authors compared effectiveness of prochlorperazine with ondansetron	▪ Difference found in the number of complete responses (symptom score improving to a 0 out of 10 regardless of previous value documented) favouring prochlorperazine (22/45 48.9% for prochlorperazine 12/45 26.7% for ondansetron) ▪ Increased number of worse responses seen with ondansetron patients ▪ Neither difference statistically significant		2-

CHLORPROMAZINE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
114	Mystakidou K et al. Comparison of tropisetron and chlorpromazine combinations in the control of nausea and vomiting in patients with advanced cancer. J Pain Symptom Manage, 1998; 15(3): 176-184	Prospective, randomised trial	168 adult patients with advanced cancer randomised to oral therapy with either (1) chlorpromazine plus dexamethasone (2) chlorpromazine plus tropisetron, (3) chlorpromazine plus dexamethasone plus tropisetron or (4) tropisetron alone	▪ Patients were monitored for up to 15 days of treatment ▪ Day 1 C+D+ T most effective achieving total control of vomiting in 17.5% patients and total control of nausea in 10% patients ▪ Day 7 total control of vomiting in 28.2% C+D, 71.8% in C+T, 87.5% in D+T+C and 65.8% in T alone ▪ Day 15 total control of vomiting 33.3% in C+D, 84.6% in C+T, 92.5% in D+T+ C and 78.9% in T alone. Total control of nausea 18% in C+D, 74.4% in C+T, 85% in D+ T+ C and 65.8% in T alone	▪ Tropisetron containing combinations produced significant control of nausea and vomiting from 3rd day onward ▪ All antiemetic drugs were well tolerated ▪ Data suggests tropisetron-containing combinations or tropisetron alone are more effective in the control of emesis in patients with advanced cancer than chlorpromazine plus dexamethasone	1-

5-HT3 ANTAGONISTS AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
115	Currow DC et al. Use of ondansetron in palliative medicine. J Pain Symptom Manage, 1997; 13(5): 302-307	Retrospective analysis	16 adult patients with nausea and vomiting. Nine patients had advanced HIV/AIDS and 7 had malignancy. Inadequate response to standard antiemetics either alone or in combination. Given ondansetron in addition to other antiemetic therapy	▪ 7/9 AIDS patients had improvement in their nausea. 6/9 had improvement in their vomiting within 48 hours of commencing therapy. ▪ Of the 6 patients with malignancy who had nausea, 5 improved and 4/5 who had vomiting showed improvement ▪ Overall 13/16 derived benefit ▪ 12/15 (80%) with nausea had a demonstrable improvement and 10/14 (71%) with vomiting also improved	▪ Treatment with ondansetron was well tolerated, onset of action was rapid and response rates were high and sustained over time	3
116	Mystakidou K et al. Comparison of tropisetron and chlorpromazine combinations in the control of nausea and vomiting in patients with advanced cancer. J Pain Symptom Manage, 1998; 15(3): 176-184	Prospective, randomised trial	168 adult patients with advanced cancer randomised to oral therapy with either (1) chlorpromazine plus dexamethasone, (2) chlorpromazine plus tropisetron, (3) chlorpromazine plus dexamethasone plus tropisetron or (4) tropisetron alone	▪ Patients were monitored for up to 15 days of treatment ▪ Day 1 C+D+ T most effective achieving total control of vomiting in 17.5% patients and total control of nausea in 10% patients ▪ Day 7 total control of vomiting in 28.2% C+D, 71.8% in C+T, 87.5% in D+T+C and 65.8% in T alone ▪ Day 15 total control of vomiting 33.3% in C+D, 84.6% in C+T, 92.5% in D+T+ C and 78.9% in T alone. Total control of nausea 18% in C+D, 74.4% in C+T, 85% in D+ T+ C and 65.8% in T alone	▪ Tropisetron containing combinations produced significant control of nausea and vomiting from 3rd day onward ▪ All antiemetic drugs were well tolerated ▪ Data suggests tropisetron-containing combinations or tropisetron alone are more effective in the control of emesis in patients with advanced cancer than chlorpromazine plus dexamethasone	1-
117	Porcel JM et al. Antiemetic efficacy of subcutaneous 5-HT3 receptor antagonists in terminal cancer patients. J Pain Symptom Manage, 1998; 15(5): 265-66	Open study	10 adult patients with terminal cancer and persistent nausea and vomiting despite therapy with other antiemetics. Either ondansetron or granisetron given SC after stopping previous antiemetic regimens except for dexamethasone	▪ 6 patients received SC ondansetron and 4 patients SC granisetron ▪ Vomiting episodes decreased dramatically in 7 patients within hours, were partially controlled in 2 and unchanged in 1 patient who had a bowel obstruction ▪ 4 patients converted to oral therapy ▪ Performance status of complete and partial responders improved significantly ▪ No adverse local reactions despite acidic pH of injection		3

5-HT3 ANTAGONISTS AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
118	Cole R et al. Successful control of intractable nausea and vomiting requiring combined ondansetron and haloperidol in a patient with advanced cancer. J Pain Symptom Manage, 1994; 9(1): 48-50	Case report		▪ Combined use of a D2-receptor antagonist (haloperidol) and a 5-HT3 antagonist (ondansetron) required in this patient to relieve intractable nausea and vomiting		3
119	Kast RE et al. Cancer chemotherapy and cachexia: mirtazapine and olanzapine are 5-HT3 antagonists with good anti-nausea effects. Eur J Cancer Care, 2007; 16(4): 351-354	Review			▪ Mirtazapine and olanzapine are psychiatric drugs with potent anti-nausea effects ▪ Like ondansetron and related compounds, mirtazapine and olanzapine are potent 5-HT3 receptor antagonists but have a longer half-life, are cheaper and may offer better and smoother 24H nausea control ▪ Mirtazapine and olanzapine can give potent nausea reduction and appetite increase in advanced cancer-related nausea ▪ Double-blind studies against ondansetron and similar compounds suggested	4
120	Srivastava M et al. Olanzapine as an antiemetic in refractory nausea and vomiting in advanced cancer. J Pain Symptom Manage, 2003; 25(6): 578-582	Case reports	2 adult cancer patients with nausea and vomiting refractory to standard antiemetics	▪ Olanzapine at an oral dose of 5mg BD resolved nausea and vomiting in both patients	▪ Receptor binding profile of olanzapine (D2, H1, Ach, 5-HT3) has potentially broad anti-emetic capabilities ▪ Weight gain and improved appetite are additional benefits in cachetic patients ▪ Olanzapine may be a good second line antiemetic for patients with nausea refractory to butyrophenones or phenothiazines or who have extrapyramidal reactions to usual antiemetics ▪ Cost less than 5-HT3 antagonists	3

HYOSCINE BUTYLBROMIDE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
121	Mercadante S et al. Medical treatment for inoperable malignant bowel obstruction: a qualitative systematic review. J Pain Symptom Manage, 2007; 33(2): 217-233	Systematic review of randomised trials that involve patients with a clinical diagnosis of intestinal obstruction due to advanced cancer and who were treated with corticosteroids, hyoscine butylbromide or octreotide	102 adult patients in 5 studies. Two studies were not blinded, 3 were double-blind (one of which was a crossover design with 5-day phases)	▪ 52 received octreotide, 51 hyoscine butylbromide, 37 corticosteroids, 15 placebo and 37 both placebo and corticosteroids ▪ 3 studies compared octreotide and hyoscine butylbromide and 2 studies compared corticosteroids and placebo ▪ Octreotide was superior to hyoscine butybromide in relieving GI symptoms in 3 studies totalling 103 patients	▪ On the basis of these studies, octreotide can be reasonably considered more effective than hyoscine butylbromide in relieving symptoms due to inoperable bowel obstruction ▪ Role of corticosteroids remains debatable due to methodological weakness of existing studies	1+
122	De-Conno et al. Continuous subcutaneous infusion of hyoscine butylbromide reduces secretions in patients with GI obstruction. J Pain Symptom Manage, 1991; 6(8): 484-486	Case report	3 patients with inoperable bowel obstruction	▪ Reduction of drainage from GI tract observed with hyoscine butylbromide infusion		3

OCTREOTIDE AS AN ANTIEMETIC IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
123	Mercadante S et al. Medical treatment for inoperable malignant bowel obstruction: a qualitative systematic review. J Pain Symptom Manage, 2007; 33(2): 217-233	Systematic review of randomised trials that involve patients with a clinical diagnosis of intestinal obstruction due to advanced cancer and who were treated with corticosteroids, hyoscine butylbromide or octreotide	102 adult patients in 5 studies. Two studies were not blinded, 3 were double-blind (one of which was a crossover design with 5-day phases)	▪ 52 received octreotide, 51 hyoscine butylbromide, 37 corticosteroids, 15 placebo and 37 both placebo and corticosteroids ▪ 3 studies compared octreotide and hyoscine butylbromide and 2 studies compared corticosteroids and placebo ▪ Octreotide was superior to hyoscine butylbromide in relieving GI symptoms in 3 studies totalling 103 patients	▪ On the basis of these studies, octreotide can be reasonably considered more effective than hyoscine butylbromide in relieving symptoms due to inoperable bowel obstruction ▪ Role of corticosteroids remains debatable due to methodological weakness of existing studies	1+
124	Watanabe H et al. Octreotide improved the quality of life in a child with malignant bowel obstruction caused by peritoneal dissemination of colon cancer. J Pediatr Surg, 2007; 42(1): 259-60	Case report	12 year old male with severe abdominal symptoms caused by incomplete bowel obstruction due to tumour progression	▪ IV octreotide infusion resulted in improvement in abdominal symptoms including resolution of nausea		3
125	Khoo D et al. Palliation of malignant intestinal obstruction using octreotide. Eur J Cancer, 1994; 30A(1): 28-30	Phase I/II study	24 adult patients with intractable vomiting secondary to intestinal obstruction due to malignant disease	▪ Vomiting controlled or volume of NG aspirate markedly reduced in 18/24 patients receiving a SC infusion of octreotide ▪ Further 2 patients had partial relief of their symptoms		2-
126	Mercadante S et al. Octreotide in relieving GI symptoms due to bowel obstruction. Palliative Med, 1993; 7(4): 295-299	Case series	14 adult patients with intestinal obstruction	▪ SC octreotide reduced the volume of GI secretions and good control of vomiting was achieved in 12 patients ▪ No major side effects		3

Constipation

Recommendations for Inclusion: SENNA, DOCUSATE SODIUM

New medicines for addition to EMLc: Docusate sodium

New formulations for addition to EMLc:
Docusate sodium oral capsules 100mg and oral solution 50mg/5ml
Senna oral syrup 7.5mg/5ml

DEFINITION

Constipation is defined as difficulty in defaecation. There is a wide range in normal bowel habit and constipation cannot simply be defined in terms of stool frequency.

SCOPE

- Management of constipation comprises identification and, if appropriate, treatment of possible underlying cause(s)
- Non pharmacological management of constipation with attention to fluid intake, nutrition and mobility is important but may be limited by anorexia and general debilitation in palliative care
- Here we consider only pharmacological management of constipation

OVERVIEW OF MANAGEMENT OPTIONS

CLASSE(S) OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

- Laxatives
  - Stimulant laxatives
  - Osmotic laxatives (stool softeners)
- Naloxone

LAXATIVES IN THE MANAGEMENT OF CONSTIPATION

Recommendations
Constipation is one of the most troublesome and persistent symptoms in palliative care patients and should be treated with laxatives [131] [132] [133] [134] [135]
An extensive literature search confirmed there is little good quality trial evidence to confirm the effectiveness of laxatives in constipation associated with palliative care in adults or children [127]
There is a lack of evidence to support the use of one laxative, or combination of laxatives, over another and choice can be related to cost effectiveness and availability as much as to efficacy [127]
Constipation is an almost inevitable consequence of opioid use. Laxatives must be prescribed for any patient receiving strong opioids [128] [129] [130]

Evidence for management of this symptom in children

- Randomized controlled trial evidence supports the efficacy of laxatives in the management of chronic functional constipation in children. However there is insufficient evidence to recommend one laxative over another.
- Evidence to support the use of laxatives in palliative care in children is limited to expert opinion

Where this alone is insufficient evidence for the management of this symptom in adults

- There is little good quality trial evidence to confirm the effectiveness of laxatives in constipation associated with palliative care in adults or children.
- In addition, there is a lack of evidence to recommend the use of one laxative, or combination of laxatives, over another.
- Constipation, due to increase in gastrointestinal transit time is an inevitable consequence of opioid use. Therefore use of a stimulant laxative appears to be the most appropriate choice in opioid induced constipation.
- Laxatives may be needed at high doses, particularly in opioid induced constipation in palliative care
- Where high dose stimulant laxative is insufficient to manage constipation expert opinion supports the use of a combination of stimulant laxative and osmotic agent.
- Bulk forming laxatives are unlikely to be appropriate in palliative care
- In the absence of any data showing greater efficacy of one agent over another, the choice of laxatives within a class for inclusion in the EMLc likely to be determined by other factors such as availability of suitable formulations, route of administration, pharmacokinetics and cost-effectiveness

Additional supporting information for this drug

SENNA

- Senna is included in the EMLc (>12 years) and safety and efficacy have been established in children less than 12 years of age.
- Senna is available in both oral liquid and oral tablet formulations.
- Senna is cheap and widely used as a stimulant laxative in children.

DOCUSATE SODIUM

- Docusate sodium is widely available and used in children with an established safety profile.
- Docusate sodium is available as both capsules and a liquid formulation
- Docusate sodium appears to be better tolerated, particularly at high doses than lactulose which is associated with bloating and colic.
- Docusate is not currently included in the EMLc or the EML.
- Approximate costs indicate a unit dose of docusate sodium (oral solution) is cheaper than lactulose.

Additional supporting information / comparative data for laxatives

	Mode of action	Routes of administration	Available formulation	Licensed status in UK/USA/Australia	Current listing in EMLc or EML	Pharmacology/ Pharmacokinetics	Approximate cost (average single day for 10 year old in UK)
Senna	Stimulant	Oral	Oral liquid Oral tablets	From 2 years of age	EML	Onset of effect: 8-12 hours	1-2 tablets daily 3-6p/day 5-10ml daily 3-6p/day
Bisacodyl	Stimulant	Oral Rectal	Oral tablets Rectal suppositories	Oral from 3-4 years Rectal – all ages	No	Onset of effect: Oral 10-12 hours Rectal 20-60 mins	Oral: 5-10mg nocte (20 x 5mg tablets ~ 50p) = 2.5-5p/day Rectal: 10mg in the morning (12 x 10mg suppositories ~ 77p) = 6.5p/day
Sodium picosulphate	Stimulant	Oral	Oral liquid Oral sachets (Picolax)	UK – all ages ? availability in USA and Australia	No	Onset of effect: 10-14 hours	5-10mg (=5-10ml of liquid) at night ~ 9-18p/day
Lactulose	Osmotic faecal softener	Oral	Oral liquid	All ages	No	Onset of effect: ~ 48 hours	10–15ml BD: 14-20p/day
Docusate sodium	Faecal softener	Oral	Oral liquid Oral tablets	UK – from 6 months; USA – from 2 years	No	Onset of effect: 12-48 hours	12.5mg/5m:l 5-10ml TDS (1 x 300ml ~ £1.60) = 8-16p/day 50mg/5ml: 2.5 - 5ml TDS (1 x 300ml ~ £2.50) = 2-4p/day Capsules 100mg/day ~ 8p/day
Co-danthramer	Stimulant	Oral	Oral liquid Oral tablets	UK only – from12 years in terminal illness only	No	Onset of effect: 6-12 hours	1 capsule at night: 20p/day 5ml at night: 50p/day
Co-danthrusate	Stimulant	Oral	Oral liquid Oral tablets	UK only – from 12 years in terminal illness only	No	Onset of effect: 6-12 hours	I capsule at night: 20p/day 5ml at night: 22p/day

NALOXONE IN THE MANAGEMENT OF OPIOID-INDUCED CONSTIPATION

Recommendations
Oral naloxone has shown some efficacy in the management of opioid-induced constipation in adults [128]
Insufficient evidence to confirm safe and effective dose and no evidence on use in children for this purpose [128]

Evidence for management of this symptom with this drug in children
No evidence has been identified in children to support the use of oral naloxone as a possible alternative to laxatives in the management of opioid-induced constipation.

Where this alone is insufficient evidence to support management of this symptom in adults
- Oral naloxone may have a role in management of opioid induced constipation.
- Small amounts of oral naloxone absorbed through the GI tract may result in acute opioid withdrawal syndrome
- Data in adults may potentially be extrapolated to children but a safe and effective dose has yet to be established in the adult population.

DRUG TREATMENT OF CONSTIPATION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
127	Miles CL et al. Laxatives for the management of constipation in palliative care patients (Review). Cochrane Database of Systematic Reviews 2006	Systematic review	Randomised controlled trials	▪ Laxatives evaluated were lactulose, senna, co-danthramer, Misrakasneham (traditional Indian herbal medicine) and magnesium hydroxide/liquid paraffin ▪ All the laxatives demonstrated a limited level of efficacy although a significant number of patients required rescue medication ▪ Only significantly different treatments were in a trial in which lactulose plus senna were more effective than co-danthramer	▪ Only 4 controlled trials (280 patients) that fulfilled the inclusion criteria were identified ▪ The treatment of constipation in palliative care is based on inadequate experimental evidence, such that there are insufficient randomised controlled trial data. Recommendations for laxative use can be related to costs at much as to efficacy	1++
128	McNicol E et al. Management of opioid side-effects in cancer-related and chronic noncancer pain: A systematic review. J Pain, 2003; 4(5): 231-256	Systematic review	Included 17 studies on opioid-induced constipation (various quality). Can be broadly divided into articles describing trials of various laxatives and articles comparing/exploring the degree of constipation in relation to a specific opioid or its route of administration	▪ 4 studies on use of laxatives (2 included in Cochrane review above) – no evidence of improved efficacy of one agent over another ▪ 4 studies of opioid antagonist naloxone. Generally naloxone effective. Optimal dose and frequency not established and some patients reported a reduction in analgesia.	▪ Included 2 of the 4 studies described in the Cochrane review	1+
129	Sykes NP. The relationship between opioid use and laxative use in terminally ill cancer patients. Palliative Med, 1998; 12: 375-382	Prospective study	498 terminally ill adult patients	▪ Laxatives required by 87% patients taking strong opioids and 74% of those taking weak opioids (and 64% of those not receiving opioids) ▪ Dose of laxative required likely to be significantly higher if an opioid is being taken than if not		3
130	Fallon MT et al. Morphine, constipation and performance status in advanced cancer patients. Palliative Med, 1999; 13: 159-160	Open study	50 terminal adults	▪ Treatment with laxatives is effective in the majority of patients ▪ No correlation between morphine dose and the dose of laxative required ▪ Persistent constipation in this population is more closely related to how ill and disabled the patient is than to their use of morphine		3
131	CKS – Constipation in Palliative Care 2008	Expert opinion			▪ Supports use of laxatives	4
132	Fallon M et al. ABC of palliative care: constipation and diarrhoea. BMJ, 1997; 315: 1293-96	Review article			▪ Supports use of laxatives	4
133	Regnard and Hockley. A guide to symptom relief in palliative care. 5th Edition	Expert opinion			▪ Supports use of laxatives	4

DRUG TREATMENT OF CONSTIPATION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
134	Twycross and Wilcock. Symptom Management in Advanced Cancer. 3rd Edition	Expert opinion			▪ Supports use of laxatives	4
135	Jassal SS. Basic symptom control in paediatric palliative care. The Rainbow Children's Hospice Guidelines. 7th Edition 2008	Expert opinion			▪ Supports use of laxatives	4

Depression

Recommendation for Inclusion: FLUOXETINE

No new medicines for addition to EMLc

No new formulations for addition to EMLc

DEFINITION

- Depression is characterized by persistent feelings of extreme sadness and low mood associated with loss of interest in activities and inability to experience pleasure. There are often associated biological features of significant changes in appetite and weight, disturbed sleep, fatigue and poor concentration.
- Depression in palliative care is likely to be significantly under-recognized and under-treated as the symptoms overlap with symptoms of the underlying condition.

SCOPE

- Treatment of pain and other reversible physical symptoms should be instituted before or concurrently with initiation of specific antidepressive treatment
- Psychological approaches to depression in palliative care, particularly cognitive behavioural therapy are important
- Anxiety commonly exists as a co-morbidity with depression. Management of anxiety is considered below
- Here we consider only pharmacological management of depression

OVERVIEW OF MANAGEMENT OPTIONS

CLASSE(S) OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

- Antidepressants
  - Tricyclic antidepressants
  - Selective serotonin re-uptake inhibitors
- Psychostimulants
  - Methylphenidate

ANTIDEPRESSANTS

TRICYCLIC ANTIDEPRESSANTS

Recommendations
Data suggest tricyclic antidepressants are not useful in treating depression in pre-pubertal children [144] [145]
Marginal evidence to support the use of tricyclic antidepressants in the treatment of depression in adolescents although the magnitude of this effect is likely to be moderate at best [144] [145]

SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

Recommendations
Safety and efficacy of the selective serotonin re-uptake inhibitors in children and adolescents is not fully established [143] [145] [146]
Use of selective serotonin re-uptake inhibitors in children and adolescents with depression has been associated with an increased risk of suicidal ideation and behaviour [143] [145] [146]
Fluoxetine is the only selective serotonin re-uptake inhibitors for which there is consistent evidence from clinical trials that it is effective in reducing depression symptoms in both children and adolescents [143] [145] [146]

Evidence for management of this symptom in children

- Fluoxetine – this is the only antidepressant for which there is consistent evidence of efficacy in children and adolescents with depression.
- The use of selective serotonin re-uptake inhibitors in children and adolescents has been associated with an increased risk of suicidal ideation and behaviour although this risk has not been shown in published and unpublished trials of fluoxetine with placebo.
- Fluoxetine does however have a prolonged time before a therapeutic effect is established and this may be a limiting factor to its use in those patients in the terminal stage.
- Evidence to support the use of antidepressants in children with depression at end of life is limited to expert opinion.

Where this alone is insufficient evidence for the management of this symptom in adults

- A systematic review of antidepressants in the management of depression in cancer and palliative care concluded that there was insufficient evidence to support the use of one antidepressant in preference to another

Additional supporting information for this drug

FLUOXETINE

- Fluoxetine is a selective inhibitor of serotonin reuptake.
- Fluoxetine has practically no affinity to other receptors such as α_1-, α_2-, and β-adrenergic; serotonergic; dopaminergic; histaminergic$_1$; muscarinic; and GABA receptors.
- In the UK and USA, fluoxetine is licensed for moderate to severe major depressive episode in children and adolescents from 8 years of age.
- Fluoxetine is available as an oral solution 20mg/5ml and 10mg, 20mg and 40mg oral capsules/tablets.
- Fluoxetine is included in the EML and the EMLc (complementary list from 8 years of age) for the treatment of depressive disorders.
- The dosage form currently listed is 20mg capsules/tablets.
- Fluoxetine can be taken as a single daily dose.

PSYCHOSTIMULANTS

Recommendations
Systematic review suggests there is insufficient evidence to recommend the use of psychostimulants above other more established treatments of depression [148]
Some evidence that in the short-term, psychostimulants reduce the symptoms of depression and may have a role in certain circumstances e.g. when established treatments for depression have failed or is rapid onset therapy is required for short-term use [148] [149] [150] [151]
No evidence to support psychostimulants for treatment of depression in children

Evidence for management of this symptom with this drug in children
No evidence has been identified to support use of psychostimulants for treatment of depression in children and their use is not recommended.

Where this alone is insufficient evidence for management of this symptom in adults
- A systematic review identified 24 trials of psychostimulants in major depression in adults concluded there was insufficient evidence for this review to recommend the use of psychostimulants above other more established treatments of depression [148]
- 3 trials (62 participants) demonstrated that oral pyschostimulants, as monotherapy, significantly reduced short term depressive symptoms in comparison with placebo with non-significant heterogeneity.
- There is some randomized clinical trial evidence to suggest that in the short-term, psychostimulants reduce the symptoms of depression and may have a role in when rapid onset therapy is required for short-term use such as in end of life care

ANTIDEPRESSANTS FOR THE TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of evidence**
136	Lan Ly et al. Depression in palliative care: a systematic review. Palliative Med, 2002; 16: 279-284	Systematic review	Randomised controlled trials that assessed treatments for depression in palliative care patients. Adults only.	▪ 3 RCTs on the treatment of depression that met inclusion criteria ▪ Of 73 women with advanced cancer, those treated with the TCA mianserin had a significant improvement in depression with no differences between the groups in terms of side effects ▪ In 40 patients with advanced cancer the SSRI fluoxetine and the TCA desipramine were equally effective in improving depression with no statistically significant difference in adverse effects ▪ In 50 terminal patients with mixed anxiety and depressive symptoms, both thioridazine and placebo showed an improvement in depression with a statistically significant difference favouring thioridazine	▪ Paucity of good data on effective treatments for depression in the palliative care population	1+
137	Lloyd-Williams M et al. A survey of antidepressant prescribing in the terminally ill. Palliative Med, 1999; 13: 243-248	Retrospective case analysis	1046 consecutive patient admissions to 4 palliative care units (1026 patients included in review)	▪ Total of 106 patients (7%) were prescribed antidepressants during their contact with the palliative care units ▪ Of these, 22 (21%) were started on antidepressant medication prior to admission (range 7 days to 4 months prior to admission) ▪ 84 patients (79%) were started on treatment during their inpatient stay ▪ 78/106 patients died within 2 weeks of starting antidepressants and of these 56 (52%) died within 1 week ▪ 26 patients were prescribed TCAs ▪ 76 patients were prescribed SSRIs ▪ No patients prescribed psychostimulants	▪ Depression regarded as a significant symptom for a quarter of adult patients admitted to a hospice and this review indicates a number of patients were not being treated ▪ Study suggests that terminally ill patients are currently receiving antidepressant medication at a stage in their terminal illness when there is little time for the medication to have an effect ▪ No comment on comparative efficacy of TCAs and SSRIs	3
138	Lawrie I et al. How do palliative medicine physicians assess and manage depression. Palliative Med, 2004; 18: 234-238	Questionnaire analysis	All UK palliative care units with a designated consultant or medical director. Adult patients	▪ On question of choice of therapy, 75% routinely prescribe SSRIs and 25% TCAs. Only 6% prescribe psychostimulants and 3% St Johns Wort ▪ No evidence that patients with a physical illness respond less well to antidepressants than other patients with depression		3

ANTIDEPRESSANTS FOR THE TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of evidence**
139	Wilson KG et al. Depression and anxiety disorders in palliative cancer care. J Pain Symptom Manage, 2007; 33(2): 118-129	Survey by Canadian National Palliative Care Association	Semi-structured interviews assessing depression and anxiety disorders of 381 adult patients receiving palliative care for cancer	▪ 93% patients (24.4%) fulfilled the criteria for at least one anxiety or depressive disorder ▪ Comorbidity between depression and anxiety disorders common with 10% participants meeting criteria for more than 1 disorder ▪ Patients with both depression and anxiety disorders tend to present with greater severity ▪ Patients with a mental disorder were more likely to be given antidepressants, benzodiazepines and neuroleptics with ~ 40% of these patients treated with antidepressants and ~ 66% with benzodiazepines ▪ The most commonly prescribed antidepressants were SSRIs and TCAs followed by venlafaxine and stimulants		3
140	Stiefel F et al. Depression in palliative care: a pragmatic report from the Expert Working Group of the European Association for Palliative Care. Support Care Cancer, 2001; 9: 477-488	Review article		▪ Undertreatment and underdetection of depression in palliative care remains a major problem ▪ Antidepressants should be started without delay once the diagnosis of major depression has been established ▪ Effectiveness studies comparing different agents are still lacking ▪ Until effectiveness or if survival time is very limited, amphetamines, benzodiazepines and neuroleptics should be considered		4
141	Razavi D et al. The effect of fluoxetine on anxiety and depression symptoms in cancer patients. Acta Psychiatr Scand 1996; 94: 205-210	Double-blind placebo-controlled study	115 adult cancer patients **(not palliative)** who fulfilled entry criteria. 45 randomised to fluoxetine and 46 to placebo	▪ 69 patients completed the study ▪ Drop-outs more frequent in fluoxetine group (15 patients of whom 7 because of side-effects) ▪ For patients who completed the study, a significant improvement on all assessment scales was observed in both treatment groups. This improvement was always greater in the fluoxetine group but only statistically significant for one symptom checklist. ▪ Frequencies of adverse effects did not differ significantly between fluoxetine and placebo groups		1+

ANTIDEPRESSANTS FOR THE TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of evidence**
142	Kersun LS et al. Depression and anxiety in children at the end of life. Pediatr Clinics North Am, 2007; 54: 691-708	General review article		▪ There are no studies that specifically evaluate treatment for depression in children at the end of life ▪ SSRIs can be considered as this is the safest class of antidepressant medication however (1) take several weeks to work (2) may be an increased risk of suicidality and patients should be closely monitored for worsening of depression or suicidality at the beginning of therapy and at times of dosage adjustment (3) no studies to confirm efficacy in this population (4) potential side effects – nausea, fever, tachycardia, sweating and more severe symptoms including confusion, seizures, coma must be considered		4
143	Hetrick SE et al. Selective serotonin reuptake inhibitors for depressive disorders in children and adolescents. Cochrane Database of Systematic Reviews 2008	Systematic review	Published and unpublished randomised controlled trials of children and adolescents aged 6-18 years with a diagnosis of depressive disorder. Trials included were those comparing the effectiveness of a SSRI with a placebo.	▪ 12 trials were eligible for inclusion with 10 providing usable data ▪ At 8-12 weeks there was evidence that children and adolescents 'responded' to treatment with SSRIs ▪ Also evidence of an increased risk of suicidal ideation and behaviour for those prescribed SSRIs ▪ **Fluoxetine was the only SSRI where there was consistent evidence from 3 trials (527 children and adolescents) that it was effective in reducing depression symptoms in both children and adolescents** ▪ Where rates of adverse events were reported, this was higher for those prescribed SSRIs	▪ **Not specific to palliative care** ▪ Review of these 12 trials highlighted limitations with the data making it difficult to answer questions about the effectiveness and safety of SSRIs in clinical practice ▪ Overall there was evidence of greater reduction in depressive symptoms with SSRIs than with placebo but the response was defined differently across trials making interpretation of this outcome difficult ▪ Children and adolescents with comorbid conditions and at risk of suicide were largely excluded from the trials so it is not apparent how this group would respond to SSRIs	1++

ANTIDEPRESSANTS FOR THE TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of evidence**
144	O'Connell HP et al. Tricyclic drugs for depression in children and adolescents. Cochrane Database of Systematic Reviews, 2002	Systematic review	Randomised controlled trials comparing the efficacy of tricyclic antidepressants with placebo in depressed people aged 6-18 years	▪ 13 trials (506 participants) were included ▪ No overall improvement with treatment compared to placebo was seen for children or adolescents ▪ A statistically significant but small benefit of treatment over placebo was seen in reducing symptoms ▪ Subgroup analyses suggest a larger benefit among adolescents and no benefit among children ▪ Treatment with a TCA caused more vertigo, orthostatic hypotension, tremor and dry mouth than placebo. No statistically significant difference was found for other possible adverse effects	▪ **Not specific to palliative care** ▪ Data suggest TCAs are not useful in treating depression in pre-pubertal children ▪ Marginal evidence to support the use of TCAs in the treatment of depression in adolescents although the magnitude of this effect is likely to be moderate at best	1++
145	Trindadae E et al. Adverse effects associated with SSRIs and TCAs: a meta-analysis. CMAJ, 1998; 159(10): 1245-52	Meta-analysis	Meta-analysis of double-blind randomised controlled trials involving at least one SSRI and one TCA. For the study of adverse effects only trials that had at least 20 patients in each arm and that reported rates of adverse effects in both arms were included	▪ 84 trials reporting on 18 adverse effects were available ▪ When data for all the SSRIs was pooled and compared with data for all the TCAS, there were 7 adverse effects that occurred statistically significantly more often with SSRIs (nausea, anorexia, diarrhoea, insomnia, nervousness, agitation and anxiety) and 5 that occurred statistically significantly more often with TCAs (dry mouth, constipation, dizziness, sweating and blurred vision) ▪ No statistically significant differences between drug classes in terms of drop-outs due to adverse effects	▪ **Not specific to palliative care** ▪ SSRIs and TCAs are both associated with adverse effects although the key effects differ between the drug classes	1+

ANTIDEPRESSANTS FOR THE TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
146	Whittington CJ et al. SSRIs in childhood depression: systematic review of published versus unpublished data. Lancet, 2004; 363: 1341-45	Systematic review	Meta analysis of data from randomised controlled trials that evaluated an SSRI versus placebo in participants aged 5-18 years and that were published in a peer-reviewed journal or were unpublished and included in a review by the CSM	▪ 5 randomised controlled trials included ▪ Fluoxetine - 2 published RCTs (315 participants aged 7-18 years) showed fluoxetine more likely than placebo to bring about remission by end of 7-8 weeks of treatment. Fluoxetine also led to a clinically meaningful treatment response and a small reduction in depressive symptoms. In terms of safety, fewer serious adverse effects were reported in the fluoxetine group. No unpublished trials of fluoxetine found but the CSM review included unpublished data on suicidal behaviour and no increased risk found with fluoxetine ▪ Paroxetine - pooling data from 1 published trial (180 participants aged 12-18 years) and 2 unpublished trials (478 participants aged 7-18 years), evidence suggests that paroxetine does not improve depressive symptoms and has little effect on response. There is an increased risk of having a serious adverse event and of suicidal ideation or attempting suicide ▪ Sertraline – 2 published RCTs (376 participants aged 6-17 years) showed sertraline was more likely than placebo to bring about a response by the end of 10 weeks of treatment but gave little improvement in mean depressive symptoms. No data for remission. Slightly more sertraline treated patients reported serious adverse events and suicide attempts or ideation. CSM review provides additional data on remission but give little support for a benefit of treatment ▪ Citalopram – no published RCTs that met review criteria. CSM review provided data from2 unpublished trials (422 participants aged 7-18 years). Efficacy data from these trials limited but suggested that citalopram was unlikely to produce a clinically important reduction in depressive symptoms by the end of 8-12 weeks of treatment. Citalopram increased the risk of attempting suicide and was associated with a small increased risk of treatment-emergent adverse events ▪ Venlafaxine – 1 small RCT (40 participants aged 8-18 years) suggested venlafaxine did not improve depressive symptoms by the end of 6 weeks of treatment; no serious adverse effects reported. Two unpublished trials included in CSM review (334 participants aged 6-17 years) again confirming a clinically important improvement in depressive symptoms unlikely with venlafaxine by the end of 8 weeks of treatment. Patients on venlafaxine had an increased risk of discontinuation because of adverse effects	▪ **Not specific to palliative care** ▪ Published data suggest a favourable risk-benefit profile for some SSRIs **however, addition of unpublished data indicates that risks could outweigh benefits of these drugs (except fluoxetine) to treat depression in children and adolescents**	1+

ANTIDEPRESSANTS FOR THE TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of evidence**
147	Usala T et al. Randomised controlled trials of SSRIs in treating depression in children and adolescents: a systematic review and meta-analysis. European Neuropsychopharmacology, 2008; 18: 62-73	Systematic review and meta-analysis	Systematic review and meta-analysis of randomised controlled trials in which an SSRI was compared to placebo in children and adolescents with depressive disorder or depressive symptoms	▪ 13 studies (2530 participants) included of which 11 met the criteria for inclusion in the meta-analysis ▪ Only fluoxetine appeared to offer a moderately significant benefit profile ▪ All studies differed in diagnostic tools and primary efficacy measures	▪ **Not specific to palliative care** ▪ SSRI treatment, especially with fluoxetine, may be effective in child and adolescent depression ▪ Additional RCTs with sound methodological designs and outcome measures necessary to determine role of SSRIs in this patient population	1++

PSYCHOSTIMULANTS FOR THE TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
148	Candy B et al. Psychostimulants for depression (review). Cochrane Database of Systematic Reviews 2008	Systematic review of randomised controlled trials assessing the effectiveness of psychostimulants in the treatment of depression and to assess adverse events associated with pyschostimulants	Adults of either sex with a diagnosis of depression (patients with serious concomitant medical illness were included in this review but not specifically palliative care)	▪ 24 RCTs identified ▪ Overall quality of the trials was low ▪ 5 drugs evaluated – dexamphetamine, methylphenidate, methylamphetamine, pemoline and modafinil ▪ Psychostimulants were administered as a monotherapy, adjunct therapy, as oral or IV and in comparison with a placebo or an active therapy ▪ Most effects were measured in the short term (up to 4 weeks) ▪ 13 trials included data suitable for meta-analysis ▪ 3 trials (62 participants) demonstrated that oral pyschostimulants, as monotherapy, significantly reduced short term depressive symptoms in comparison with placebo with non-significant heterogeneity. A similar effect was found for fatigue. However, overall quality of trials poor. ▪ In the short term, psychostimulants were acceptable and well tolerated ▪ Modafinil was evaluated separately (due to difference in pharmacology) and no statistically significant difference in depression symptoms was found between modafinil and placebo	▪ Not palliative care ▪ **Insufficient evidence for this review to recommend the use of psychostimulants above other more established treatments of depression** ▪ Some evidence that in the short-term, psychostimulants reduce the symptoms of depression and may have a role in certain circumstances e.g. when established treatments for depression have failed or is rapid onset therapy is required for short-term use ▪ This reduction reaches statistical significance but clinical significance is less clear ▪ However, as a result of heterogeneity in pyschostimulant intervention and comparative treatments, and the paucity of RCTs with sufficient data for qualitative analysis, few clinically relevant conclusions can be drawn	1++
149	Homsi J et al. A phase II study of methylphenidate for depression in advanced cancer. Am J Hospice and Palliative Care, 2001; 18(6): 403-407	Open-label prospective study	41 adult patients with advanced cancer given methylphenidate	▪ 30 patients completed study (methylphenidate stopped in 6 patients because of adverse effects and 5 were not evaluable) ▪ 21 responded to 10mg/day on day 3; the other 9 responded to 20mg/day on day 5 ▪ 29 patients maintained their positive response through day 7 ▪ Anorexia, fatigue, concentration and sedation improved in some ▪ All patients who completed the study had tolerable side effects, none of which caused treatment to stop	▪ Methylphenidate appeared effective for depression in advanced cancer with a starting dose of 10mg daily in divided doses being effective in most patients ▪ Improvement occurs within 3 days ▪ Short term efficacy only	3

PSYCHOSTIMULANTS FOR THE TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
150	Woods SW et al. Psychostimulant treatment of depressive disorders secondary to medical illness. J Clin Psychiatry, 1986; 47(1): 12-15	Review of hospital charts	66 adult medical and surgical patients who received dextroamphetamine or methylphenidate to treat a depressive disorder	▪ ~ ¾ showed some improvement with psychostimulant therapy ▪ ~ ½ showed marked or moderate improvement ▪ Of those who improved, 93% reached peak response within first 2 days	▪ Psychostimulants appear to be a therapeutic option in medically ill depressed population with faster onset of effect than more traditional therapies ▪ However, duration of response only short	3
151	Macleod AD. Methylphenidate in terminal depression. J Pain and Symptom Management, 1998; 16(3): 193-198	Prospective open study / case series	26 adult hospice patients diagnosed as clinical depressed and treated with methylphenidate. Patients commenced on 10mg daily, increasing to 20mg daily if no response after 48 hours. Irrespective of clinical response, methylphenidate was stopped within 6 weeks of starting or 3 weeks after a response	▪ 46% achieved a favourable mood response ▪ Of those who survived longer than 6 weeks, 50% made a significant response compared to only 7% who dies within 6 weeks of commencing methylphenidate ▪ Moderate or marked response achieved by 50% women and only 12% men ▪ Side effects not problematic in this group	▪ Efficacy of psychostimulants may diminish with disease progression ▪ Psychostimulants may have a role alongside a conventional antidepressant to overcome lag to response time of latter agents	3

Excess respiratory tract secretions/ death rattle

Recommendation for Inclusion: HYOSCINE HYDROBROMIDE

New medicines for addition to EMLc: Hyoscine hydrobromide

New formulations for addition to EMLc:
Hyoscine hydrobromide transdermal patch 1mg / 72 hours and injection
400 microgram/ml and 600 microgram/ml

DEFINITION

Death rattle is a term used to describe a rattling noise produced by accumulated secretions in the airway which oscillate in time with inspiration and expiration. Generally death rattle is seen only in patients who are extremely weak and close to death.

SCOPE

- Death rattle is associated with decreased consciousness and associated depression of cough and swallow reflexes at end of life. The patient is unlikely to be aware of, or distressed by, accumulated respiratory secretions.
- Management of death rattle is therefore primarily for the benefit of those present in the last hours and days.
- Non pharmacological management of death rattle includes positioning (and in some cases oropharyngeal suction) to reduce accumulation of secretions
- Here we consider only pharmacological management of death rattle

OVERVIEW OF MANAGEMENT OPTIONS

CLASSE(S) OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

- Antimuscarinic (anticholinergic) drugs

ANTIMUSCARINIC DRUGS IN THE MANAGEMENT OF DEATH RATTLE

Recommendations
Antimuscarinic drugs (hyoscine hydrobromide, hyoscine butylbromide and glycopyrronium) can be effective in drying of respiratory secretions but there is no substantial evidence from systematic review, that any intervention, be it pharmacological or non-pharmacological is superior to placebo in the treatment of death rattle [152] [154] [155]
Lack of conclusive evidence of comparative efficacy of these three agents – no optimal drug or dosage regime established [152] [154] [155] [156] [157]

Evidence for management of this symptom with this drug in children

- No evidence base was identified for use of antimuscarinic agents to control excessive respiratory secretions in children in the palliative care setting.
- Evidence for the use of antimuscarinic drugs in the management of death rattle in children is limited to expert opinion
- There is considerable experience in the use of antimuscarinic drugs in the management of excess salivation and drooling in children with neurodisability

Where this alone is inadequate evidence for management of this symptom in adults

- Antimuscarinic drugs reduce the production of saliva and have some effect on reducing respiratory secretions.
- Antimuscarinic drugs are less likely to be effective when secretions are the result of lung abnormalities (e.g. bronchial secretions) or reflux of gastric contents.

- A systematic review identified one randomized placebo-controlled trial of the use of hyoscine hydrobromide. Use of hyoscine hydrobromide reduced the incidence and severity of death rattle but the result did not reach statistical significance
- In the absence of any data showing greater efficacy of one agent over another, the choice of antimuscarinic for management of death rattle in the EMLc palliative care is likely to be determined by other factors such as availability of suitable formulations, route of administration, pharmacokinetics and cost-effectiveness

Additional supporting information for this drug

HYOSCINE HYDROBROMIDE

- In the UK, hyoscine hydrobromide is available in formulations for administration by oral, transdermal and parenteral routes and is generally the agent of first choice to control excessive secretions.
- Hysocine hydrobromide can cause sedation (this may be a useful or an unwanted adverse effect) and agitation.

Additional supporting information/comparative data for these drug(s)

	Route(s) of administration	Formulations	Licensed status in UK, USA and Australia	Current listing in EMLc or EML	Pharmacology / Pharmacokinetics	Cost	Other potential roles in palliative care
Hyoscine hydrobromide	Oral Transdermal Parenteral	Oral tablets Transdermal patch Injection	UK- tablets >3 years and patches >10 years for motion sickness; injection as a premed – all ages	No	**Tertiary amine** Rapidly absorbed across BBB – may cause sedation (may be desirable) and agitation **Relatively short duration of action (<1 hour) following single SC dose but effect prolonged with repeated doses**	Continuous SC infusion @ 1.2mg/day ~ £5.00/day	Antiemetic
Hyoscine butylbromide	Parenteral (oral not effective in this indication)	Injection	Injection – not licensed in children in UK; does not appear readily available in USA or Australia as this salt	No	**Quaternary amine** Does not cross BBB so does not have a central anti-emetic action or cause drowsiness **Poor oral bioavailability** Relatively short duration of action (<2 hours) following single SC dose but effect prolonged with repeated doses	Continuous SC infusion @ 60-120mg/day ~ 60p - £1.20/day	Analgesia in smooth muscle spasm Inoperable bowel obstruction
Glycopyrronium bromide	Oral Parenteral	Oral tablets Injection	Injection – all ages as a premed	No	**Quaternary amine** Poor penetration of BBB so rarely causes sedation or delirium **Longer duration of action (6-7 hours) following single SC dose than hyoscine preparations** Slower onset of action than hyoscine **Less cardiac side effects than hyoscine because of reduced affinity for muscarinic type 2 receptors**	Continuous SC infusion @ 1.2mg/day ~ £3.00/day	Inoperable bowel obstruction

ANTIMUSCARNINIC DRUGS IN THE TREATMENT OF RESPIRATORY SECRETIONS IN PALLIATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
152	Wee and Hillier. Interventions for noisy breathing in patients near to death. Cochrane Database of Systematic Reviews 2008	Systematic review	Adults and children with noisy breathing at the end of life. Identified studies were RCTs, controlled before and after studies or interrupted time series and of 10 or more subjects. Studies were included if there was a pharmacological and or non-pharmacological intervention	▪ 30 studies identified but only 1 met the inclusion criteria ▪ Included study was a randomised placebo-controlled trial of the use of hyoscine hydrobromide – HH tended to reduce death rattle compared with placebo but this was not significant	▪ Currently no evidence to show that any intervention, pharmacological or non-pharmacological, is superior to placebo in the treatment of death rattle ▪ A larger randomised study comparing atropine, hyoscine butylbromide and hyoscine hydrobromide is in progress	1++
153	CKS Guidelines – Palliative cancer care: respiratory secretions at the end of life. 2007	Clinical guidelines based on literature review and expert opinion			Supports use of antimuscarinics	4
154	Hugel H et al. Respiratory tract secretions in the dying patient: a comparison between glycopyrronium and hyoscine hydrobromide. J Palliative Med, 2006; 9(2): 279-284	Comparative, matched sample study of 72 terminal adult patients (36 glycopyrrolate and 36 HH) treated for respiratory tract secretions	72 terminally ill adults (matched for age, diagnosis and gender). Study investigated the effectiveness of glycopyrronium versus HH in controlling respiratory tract secretions in patients treated according to the Liverpool Care of the Dying Pathway.	Overall, 100% patients had some response to glycopyrronium compared to 78% to HH 26 (72%) patients in glycopyrronium group were symptom-free at death, 10 (28%) had a transient response and died with respiratory tract secretions In the hyoscine group, 21 (58%) patients were symptom free at death, 7 (20%) had a transient response and 8 (22%) had no response (44% died with respiratory tract secretions) Significant difference in overall response between the 2 groups ($p<0.01$)	Overall, glycopyrronium appeared to be at least as effective as HH No statistically significant difference in response to the 2 drugs at 4 hours after onset of respiratory tract secretions No statistically significant difference in the levels of agitation between the 2 groups	2-

ANTIMUSCARNINIC DRUGS IN THE TREATMENT OF RESPIRATORY SECRETIONS IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
155	Bennett M et al. Using antimuscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care. Palliative Med, 2002; 16: 369-374	Review of current literature	Literature search to 2001 from which evidence was summarised and graded	• Remains a lack of conclusive evidence of comparative efficacy of different antimuscarinic drugs and therefore, no particular regime can be determined to be optimal. • Low doses of antimuscarinics will readily inhibit salivary secretion but have a much lesser effect on bronchial secretions • In general IV route results in faster onset but shorter duration of action than IM route • Clinically, around ¾ patients with death rattle receive antimuscarinic drugs and beneficial response seen in ~80% • Higher response rates seen in studies in which drug therapy combined with conservative interventions • Glycopyrronium has little effect on heart rate at lower doses (200microgram) but higher doses (400microgram) can result in bradycardia. Hyoscine butylbromide results in tachycardia in a dose-dependent fashion. Doses of 200microgram hyoscine hydrobromide can cause bradycardia. • All agents cause mouth dryness and can result in urine retention	• Optimal drug regimen has not been determined • Author suggests an initial SC bolus of 1 of the 3 agents; if effective at review after 30 minutes, give SC infusion.	2++
156	Hughes A et al. Audit of three antimuscarinic drugs for managing retained secretions Palliative Med, 2000; 14: 221-222	Prospective comparative audit	Audit of 3 clinical guidelines in adult patients (37 for each guideline) with advanced cancer. Initial SC therapy with (1) hyoscine hydrobromide (2) hyoscine butylbromide (3) glycopyrrolate	Single dose of any of the 3 drugs led to an improvement in 35-54% patients A smaller proportion of patients responded to the first dose of HH (35%) compared to HB (54%) or glycopyrrolate (46%) Fewer patients responded and remained settled within the first 3 doses of HH (32%) compared to HB (38%) and glycopyrrolate (49%) HH seemed to have a shorter duration of action when given by SC bolus	• Included in review above by Bennett • Overall, 54-65% patients had their secretions alleviated with no clear difference between the 3 drugs • Antimuscarinic drugs less effective for bronchial or pulmonary secretions	2-

ANTIMUSCARNINIC DRUGS IN THE TREATMENT OF RESPIRATORY SECRETIONS IN PALLIATIVE CARE: SUMMARY OF EVIDENCE (contd)						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
157	Back IN et al. A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. Palliative Med, 2001; 15: 329-337	Prospective analysis comparing efficacy of hyoscine hydrobromide and glycopyrrolate in treatment of death rattle. During phase I, patients with death rattle received HH and during phase II glycopyrrolate	Phase I – reported on 128 patients with death rattle who received SC hyoscine (bolus followed by infusion) Phase II – reported on 63 patients with death rattle who received SC glycopyrrolate (bolus followed by infusion)	• Significantly fewer patients had reduced noise scores 30 minutes after the first injection with glycopyrrolate (27%) than with HH (56%)(P=0.002) • This reduced efficacy was also reflected in the increased number of second injections needed after 30 minutes • % who responded cumulatively with glycopyrrolate after 60 minutes increased to nearer the expected overall response rate of ~50% and at this stage there was no statistically significant difference between the 2 phases	• Included in review above by Bennett • Glycopyrrolate has a slower onset of action than HH; delay in onset may be significant (a) for patient and relative distress (b) suggestion that control of death rattle is more likely to be successful if treatment is effective early • Suggestion that in this study, the initial dose of glycopyrrolate may have been too low – a higher dose (equipotent with dose of HH) may have shown better initial response	2-
158	Bennett M. Death rattle: an audit of hyoscine use and review of management. J Pain and Symptom Management, 1996; 12(4): 229-233	Retrospective study	Review of case notes of 100 consecutive deaths of adult patients of which 96 were suitable for evaluation	26 (27%) patients received infused HH at death 48 (50%) had HH in some form during last 48 hours before death In final 6 hours before death 43 (45%) received HH in some form Patients who had been in the hospice for greater than 1 week and who had cerebral malignancy were most likely to be given HH for death rattle	Unlikely that HH can control all instances of death rattle. Most effective in type I (i.e. predominantly salivary secretions accumulated very near death when swallowing reflexes inhibited). Likely to be less effective in type II (predominantly bronchial secretions accumulating over several days as patient deteriorates and becomes too weak to cough effectively) – if used HH therapy should be started as early as possible	3
159	Jassal SS et al. Basic Symptom Control in paediatric Palliative Care. The Rainbows Children's Hospice Guidelines 7th Edition 2008	Expert opinion				4

Anxiety

Recommendations for Inclusion: DIAZEPAM AND MIDAZOLAM

New medicines for addition to EMLc: Midazolam

New formulations for addition to EMLc:
Midazolam injection 1mg/ml and 5mg/ml
Diazepam rectal tubes 2.5mg, 5mg and 10mg

DEFINITION

- Anxiety is characterized by excessive feelings of fear apprehension and worry. Anxiety may be associated with symptoms of depression, poor concentration, insomnia, irritability, panic attacks, sweating, tremor and nausea.
- Significant anxiety at end of life and in children is likely to be significantly under-recognized and under-treated as the symptoms may be attributed an appropriate reaction to the underlying terminal illness.

SCOPE

- Pharmacological treatment of anxiety in palliative care is only appropriate when any precipitating factors have been identified and addressed
- Pharmacological management should be accompanied by appropriate non pharmacological measures including management of distressing symptoms, use of relaxation techniques, counselling and psychotherapy.
- Here we consider only pharmacological management

OVERVIEW OF MANAGEMENT OPTIONS

CLASS OF DRUGS APPROPRIATE FOR PHARMACOLOGICAL MANAGEMENT OF THIS SYMPTOM IN CHILDREN

- Benzodiazepines

BENZODIAZEPINES IN ANXIETY OF PALLIATIVE CARE

Recommendations
Benzodiazepines are considered the mainstay of therapy in the management of anxiety in palliative care [161] [163] [164] [165]
There are no good quality studies on the role of benzodiazepines (or other drugs) in the treatment of anxiety associated with terminal illness to draw a conclusion about their efficacy [160]
Evidence of use in children is based on expert opinion [162] [166] [167] [168]
There are no studies comparing the safety and efficacy of one benzodiazepine over another

Evidence for management of this symptom with this drug in children
The use of benzodiazepines to control anxiety in children is based on expert opinion and clinical experience.

Where this alone is insufficient evidence for management of this symptom in adults

- A systematic review failed to identify sufficient evidence to draw any conclusion about the effectiveness of pharmacotherapy in terminally ill adults
- The majority of literature on drug therapy for anxiety in palliative care is anecdotal
- There are no studies comparing the safety or efficacy of one benzodiazepine over another. The choice(s) of agent for inclusion in the EMLc is therefore likely to be determined by availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.

Additional supporting information for benzodiazepines

- No evidence of improved efficacy of one benzodiazepine over another was identified.
- The choice(s) of benzodiazepine for inclusion in the EMLc is therefore likely to be determined by availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.
- Lorazepam may be preferred to diazepam for treating acute attacks because of the rapid onset of effect when administered sublingually and it also tends to cause less sedation.
- Diazepam may be more appropriate for chronic anxiety symptoms because of its medium to long half life.
- Midazolam injection can be administered bucally if rapid onset is required.
- A continuous SC infusion of midazolam may be of use in the last few days or hours of life.
- Midazolam is water soluble and compatible with most other medicines commonly administered by continuous infusion for symptom control at the end of life

Additional supporting information/ comparative data for benzodiazepines

	Route of administration	Formulations	Licensed status in UK, USA and Australia	Current inclusion in EMLc or EML	Pharmacology / Pharmacokinetics	Cost	Other potential roles in palliative care
Diazepam	Oral Rectal Parenteral (IV only)	Oral tablets Oral liquid Injection Rectal tubes	All ages – sedation; pre-med; acute muscle spasm; convulsions; acute anxiety/agitation	Injection 5mg/ml and oral tablets 5mg as pre-operative medication and sedation for short procedures and as an anticonvulsant	**Injection not suitable for SC administration** Wide therapeutic index (wide margin of safety against toxicity) **High oral bioavailability (~100%)** Onset of action following oral administration ~15 mins **Plasma half life 20-100 hours; active metabolite nordiazepam 30-200 hours** Duration of effect 3-30 hours (slow / fast metabolisers)	Oral @ 2-10mg/day ~ 4-20p/day Rectal @ single dose of 5mg ~ £1.30	Adjunct analgesic in smooth muscle spasm Convulsions
Midazolam	Parenteral (SC or IV) Injection may be administered by buccal or oral routes (unlicensed)	Injection	All ages - sedation	No	**Not readily available as an oral or buccal formulation but the injection solution can be administered by these routes** Midazolam injection is highly water soluble enabling administration by SC injection and infusion **Midazolam is compatible with most of the drugs commonly administered by SC syringe driver** In single doses for sedation, midazolam is 3x as potent as diazepam; as an anticonvulsant it is 2x as potent. With multiple doses, diazepam gains potency due to its prolonged half-life **Buccal bioavailability ~75%; oral bioavailability ~45%** Onset of action: SC 5-10 mins; oral 60 mins; buccal within 15 minutes **Short acting with plasma half life 2-5 hours (extended by continuous SC infusion to ~10 hours)**	SC infusion @ 15-30mg/day ~ 90p - £1.80/day	As a parenteral benzodiazepine in muscle tension/spasm; terminal agitation; convulsions
Lorazepam	Oral Parenteral (IV)	Oral tablets Oral liquid (some countries) Injection	All ages – status epilepticus; Anxiety: – oral from 5 years in UK and 12 years in USA, injection from 12 years in UK and 18 years in USA	No	**Injection not recommended for SC administration** Injection can be administered by the sublingual route **Oral bioavailability ~93%** Onset of action 5 mins SL and 10-15 mins orally **Plasma half-life much shorter than diazepam (12-15 hours) but duration of effect does not correlate with plasma concentrations and can be longer (upto 72 hours)**	Oral @ 2-6mg/day ~ 40p - £1.20/day IV infusion @ 4-12mg/day ~ 40p -£1.20/day	Convulsions

BENZODIAZEPINES IN THE TREATMENT OF ANXIETY IN PALLATIVE CARE: SUMMARY OF EVIDENCE						
#	**Reference**	**Study type**	**Subjects**	**Results**	**Comment**	**Grade of Evidence**
160	Jackson KC and Lipman AG. Drug therapy for anxiety in palliative care. Cochrane Database of Systematic Reviews 2004	Systematic review	Prospective randomised trials with or without blinding involving the use of pharmacological agents for the treatment of anxiety at the end of life	▪ No study met the inclusion criteria ▪ No data available to enable any assessment to be made	▪ Remains insufficient evidence to draw a conclusion about the effectiveness of pharmacotherapy for anxiety in terminally ill patients ▪ Majority of literature on drug therapy for anxiety in palliative care is anecdotal	1++
161	Henderson M et al. The use of benzodiazepines in palliative care. Palliative Med, 2006; 20: 407-412	Retrospective review	Review of frequency and nature of benzodiazepine prescribing in 93 adult patients who had died or been discharged from a hospice	▪ 54 patients (58%) were prescribed benzodiazepines ▪ Anxiety/agitation most common indication ▪ Midazolam most commonly used followed by lorazepam and temazepam	▪ Supports use of benzodiazepines	3
162	Kersun LS et al. Depression and anxiety in children at the end of life. Pediatr Clinics North Am, 2007; 54(5): 691-708	Review article			Supports use of benzodiazepines	4
163	Barraclough J. ABC of palliative care: depression, anxiety and confusion. BMJ 1997; 315: 1365-68	Review article			Supports use of benzodiazepines	4
164	Twycross R et al. Symptom management in advanced cancer. 3rd Edition	Expert opinion			Supports use of benzodiazepines	4
165	Regnard and Hockley. A guide to symptomatic relief in palliative care. 5th Edition	Expert opinion			Supports use of benzodiazepines	4
166	BNFc 2007	Expert opinion				4
167	Goldman A. Care of the dying child. 1994	Expert opinion			Supports use of benzodiazepines	4
168	Jassal SS. Basic symptom control in paediatric palliative care. The Rainbow Children's Hospice Guidelines. 7th Edition 2008	Expert opinion			Supports use of benzodiazepines	4

Appendix 1

SIGN Levels of Evidence

1++	High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies eg case reports, case series
4	Expert opinion